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Efficacy and safety of a multi-ingredient dietary supplement (Glucocil®) in prediabetics: A randomized, double-blind, placebo-controlled study

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ABSTRACT

Background: Interest in natural food supplements as effective alternative therapeutics for managing dysglycemia has grown substantially over the past decade owing to their minimal side effects and holistic health rejuvenation.

Objective: In the present randomized, double-blind, placebo-controlled 90-day study, the efficacy of Glucocil®, a proprietary formulation of 14 natural ingredients, was investigated in a cohort of 37 pre-diabetic individuals (21 experimental and 16 placebo).

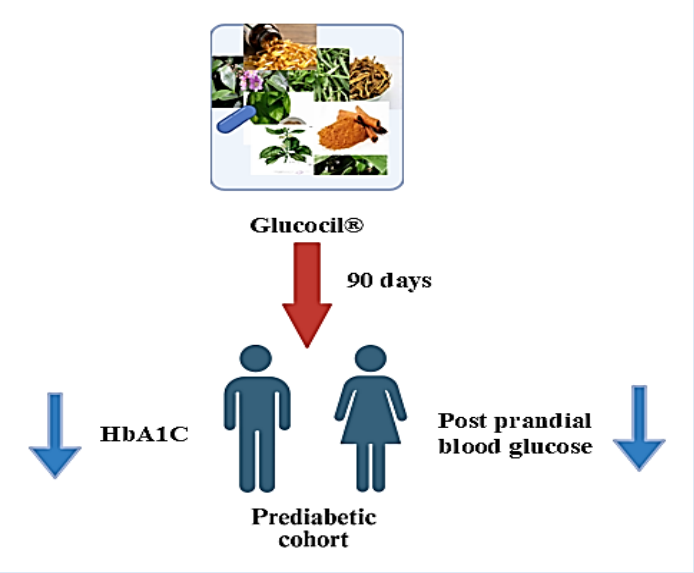
Materials and Methods: Glucocil® was bio-engineered using a proprietary manufacturing technology utilizing safety-affirmed ingredients and progressive high-shear wet milling operation with sequential addition of selected phytoconstituents, vitamins and other ingredients. Subjects were advised to consume 4,800 mg of either placebo (soybean oil; 1,200 mg/ soft gel) or Glucocil® soft gels (1,200 mg/soft gel) each day over a period of 90 consecutive days. Either at the end of the study or at intermittent intervals of 30 and 60 days, fasting blood glucose, oral glucose

tolerance, fasting insulin, glycated hemoglobin levels as well as lipid profile were assessed to ascertain the efficacy of the formulation. Anthropogenic parameters were also determined to ascertain the visible changes (if any) inflicted by the formulation. Lastly, safety of the formulation was assessed in terms of cardiovascular parameters and liver function parameters.

Results: HbA1c decreased from 6.44 to 5.80 in the Glucocil® group with significant within-group improvement (p=0.0002), whereas placebo decreased from 6.22 to 6.06 without significant within-group change (p=0.2930). The mean HbA1c change was greater with Glucocil® (−0.64) than placebo (−0.17), with a significant between-group difference (p=0.0301). OGTT 2-hour glucose decreased significantly within the Glucocil® group (−24.11 mg/dL; p=0.0131), but not significantly versus placebo between groups (p=0.5406). However, both fasting insulin and fasting blood glucose didn't undergo an equally appreciable drop. Consumption of Glucocil® did not bring about any appreciable change in body weight or other anthropometric factors. No noticeable change was found in lipid profile of the individuals in the treatment group as compared to the placebo group, except for a slight increase in HDL effected by consumption of Glucocil®. Safety assessment of this formulation was carried out in terms of assessment of cardiovascular (pulse rate, systolic and diastolic blood pressure) and liver function parameters.

Conclusion: This investigation provided valuable insights in evaluation of safety and efficacy of Glucocil®, a novel antidiabetic supplement made fully from natural ingredients and free from any noticeable side effects.

Keywords: Glucocil®- A novel phytonutrient formulation; Clinical trial; Pre-Diabetics; Blood glucose; HbA1c; Metabolic health; Safety



Graphical Abstract: Efficacy and safety of a multi-ingredient dietary supplement (Glucocil®) in prediabetics

INTRODUCTION

Diabetes has climbed up to the rank of the 7th largest silent killer in the United States at an unprecedented pace. An estimated 38.4 million people (11.6%) have been affected with diabetes to date, and ~98 million adults (more than 1 in 3) have been diagnosed with prediabetes [1]. It is quite apparent that an important step to check the progression of diabetes is to arrest and revert the physiological changes at the prediabetes stage. According to the criteria laid down by the Centers of Disease Control, prediabetes is commonly defined as HbA1c level between 5.7–6.4%, fasting plasma glucose of 100–125 mg/dL, and/or 2-hour glucose of 140–199 mg/dL (after a 75 g OGTT), with elevated risk of progression to type 2 diabetes. Estimates suggest that ~15%–30% of prediabetic patients progress to Type 2 diabetes within 5 years without effective lifestyle change, with many more progressing eventually thereafter at any stage of their lives. HbA1c, which reflects average glycemia over the prior 2–3 months, is the primary standard for assessing glycemic status and diagnosis. HbA1c integrates both fasting/basal and postprandial glucose exposure. At lower HbA1c levels (prediabetes/early diabetes), postprandial glucose typically contributes more to overall hyperglycemia, whereas fasting glucose becomes more influential as hyperglycemia worsens [2]. This is relevant for prediabetes interventions, where reducing postprandial excursions may translate into meaningful HbA1c improvement.

Type 2 Diabetes is a chronic metabolic disorder characterized by more elevated glycemia (HbA1c 6.5 or higher; fasting blood glucose greater than or equal to 126 mg/dL; 2-hour glucose 200 mg/dL or higher after a 75 g OGTT). Impaired insulin signaling jeopardizes the metabolic homeostasis which eventually leads to a plethora of physiological disorders and diseases including coronary heart disease (CHD), retinopathy, nephropathy and neuropathy [3]. If there is no genetic predisposition, the onset of Type 2 Diabetes can be arrested, even from prediabetes stage by a reversal of poor lifestyle and dietary habits. Therapeutic interventions to reverse hyperglycemia or arrest diabetes including glucagon-like peptide 1 receptor agonists, dipeptidyl peptidase-4 inhibitors, and the sodium-glucose cotransporter 2 inhibitors have met with adverse side effects including pancreatitis, cardiovascular failure, impairments in functioning of the gastro-intestinal pathway and compromised renal functioning [4]. Under the circumstances, the demand for alternative therapeutic approaches mostly based on natural products has seen an unprecedented rise over the last few decades [5,6].

The antidiabetic effects of plant extracts such as Cassia cinnamon (*Cinnamomum cassia*) [7], Fenugreek (*Trigonella foenum-graecum L*) [8] Ginseng (*Panax sp.)* [9] have been well recognized as traditional wisdoms. Most of these plant extracts are enriched in bioactive compounds which exert their effects by multiple mechanisms including increasing insulin sensitivity, reducing glucose absorptions, augmenting glucose uptake, regulating gluconeogenesis, mitigating oxidative stress and preventing dyslipidemia [10-12]. Apart from the phytotherapeutics, other natural food supplements such as α-lipoic acid (ALA, found in abundance in red meat and certain vegetables like spinach, peas, broccoli and tomatoes), mulberry leaf extract, Berberine (the primary effector molecule of the traditional Chinese herb *Coptis chinensis* French), omega-3-polyunsaturated fatty acids, and certain vegetables are also some of the well-recognized antidiabetic agents.

In the present work, the antidiabetic efficiency of Glucocil®, a proprietary blend of 14 such natural ingredients with proven roles in holistic restoration of physical wellness and metabolic homeostasis has been studied in a cohort of prediabetic individuals. Glucocil® is a combination of Vitamin B1, B6, B12, D3, chromium

picolinate, proprietary mulberry leaf extract, cinnamon bark powder, *Gymnema sylvestre* extract, Insulina (*Cissus sicyoides*) leaf extract, alpha-lipoic acid, Phellodendron bark extract (Berberine HCl), *Cissus quadrangularis* extract, Banaba leaf extract, and fish oil. Although the therapeutic properties of the individual components of this formulation are well known, no study has been conducted till date on the synergistic potential of all of them. α-lipoic acid is a potent antioxidant which can effectively reduce fasting blood glucose (FBG) levels and improve insulin sensitivity in type 2 diabetic individuals [13]. Mulberry (*Morus alba L.*) leaf has a multitude of health benefits with proven roles in glycemic regulation chiefly attributable to its bioactive 1-deoxynojirimycin, flavonoids, phenolics, and polysaccharides [14], [15]. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are the two abundant marine n-3 polyunsaturated fatty acids (PUFAs) found in fish oil implicated in minimizing CVD risk factors, alleviating inflammation and promoting healthier cognitive aging [16]. Additionally, they also promote insulin signaling and decreaseT2DM propensity. Berberine is a quaternary isoquinoline alkaloid which acts as regulator of glucose homeostasis [17]. Vitamin B complexes B1, B6 and B12 pay a major role in prevention of microvascular complications of diabetes [18]. *Gymnema sylvestre*, popularly known as cowplant, or Gurmar in India exerts its antidiabetic efficacy [19] by stimulating the regeneration of pancreatic beta cells [20]. Cinnamon (*Cinnamomum zeylanicum* and *Cinnamon cassia*) bark powder contains procyanidins and catechins which also serve as anti-glycemic agents besides having anti-oxidative and anti-inflammatory roles [21]. *Cissus quadrangularis Linn*., commonly known as veldt grape is more popular as a medicine for skin infections, constipation, piles, anemia, asthma, irregular menstruation, burns, and wounds. However, its role as a free radical scavenger and a hypoglycemic agent has led to its exploration as an anti-diabetic agent [22]. Leaves from Banaba (*Lagerstroemia speciosa L*.) has been used as a folk medicine to treat diabetes in southeast Asia as well as the rest of the world [23]. The hypoglycemic potential of this plant is chiefly attributable to corosolic acid and ellagitannins [24], [25]. Lastly, chromium (picolinate) used in this formulation has been known to augment insulin sensitivity and reduce glycosylated Hb level significantly [26]. The studies investigate the clinical efficacy of this proprietary formulation in the chosen cohort of prediabetic individuals.

MATERIALS AND METHODS

Glucocil®, a proprietary formulation of Neuliven Health: This study investigated a novel, proprietary, phytoceutical formulation Glucocil® (Composition: Vitamin B1, B6, B12, D3, chromium picolinate, proprietary Mulberry leaf extract, Cinnamon bark powder, *Gymnema Sylvestre* extract, Insulina (*Cissus Sicyoides*) leaf extract, alpha-lipoic acid, Phellodendron bark (*Phellodendron amurense*) extract (Berberine HCL), *Cissus quadrangularis* extract, Banaba leaf (*Lagerstroemia speciosa*) extract, and fish oil (Batch No S23H057, Mfg Date Jan 29, 2024). Softgel manufacturer: Robinson Pharma Inc., Santa Ana, CA, USA, a GMP-NSF certified facility in this investigation. Safety affirmed ingredients were used in manufacturing Glucocil®.

Glucocil® Manufacturing Technology*:* Glucocil® was bio-engineered using a proprietary manufacturing technology utilizing safety-affirmed ingredients. Progressive high-shear wet milling operation was performed with sequential addition of selected phytoconstituents, vitamins and other ingredients, which were uniformly homogenized as outlined in the manufacturing dossier. Finally, the combined ingredients were uniformly dispersed in fish oil. Quality control and quality assurance were strictly enforced for producing top quality finished products, which were then encapsulated in soft-gel capsules

Table 1. Phytopharmaceutical constituents in Glucocil® and potential health benefits.

Ingredients	Chemical constituents	Health Benefits
Vitamin B1 (Thiamin)	Thiamin, a water-soluble vitamin	Glucose metabolism; nerve, muscle, and cardiovascular function; and supports the body to convert carbohydrates to energy [27]
Vitamin B6 (Pyridoxine)	Pyridoxine, a water-soluble vitamin	Essential for several enzymatic reactions; promote neuronal and immune functions; metabolize proteins, fats, and carbohydrates, generate neurotransmitters including serotonin and dopamine; and biosynthesize hemoglobin to carry oxygen in red blood cells [28x].
Vitamin B12	Cobalamin, a water-soluble vitamin	Maintain brain functions; Synthesize healthy red blood cells and prevents megaloblastic anemia; Acts as coenzyme in nucleic acid biosynthesis; converts food into energy [29].
Vitamin D3	Cholecalciferol, a fat-soluble vitamin	Helps absorb calcium to construct healthy and strong bones, muscles and teeth; Boosts immune competence [30].
Chromium picolinate	Chromium (III) trispicolinate or tris(2-pyridinecarboxylato-N_1,O_2) chromium	Boosts insulin sensitization and regulates blood sugar levels; Suppresses appetite; Enhances calorie burning; Boosts overall metabolic homeostasis by regulating blood glucose, cholesterol, and body weight [31].
Morus alba (Mulberry) Extract	Phenolic acids; Flavonoids; Stilbenes, Alkaloids; Anthocyanins; Rutin; Chlorogenic acid; Resveratrol, Moracins (phosphodiesterase-4 inhibitor); Kuwanons; Vitamin C; Vitamin K; Potassium; Iron; and high levels of protein, fiber, and minerals.	Offers potent antioxidant and anti-inflammatory benefits; Reduces Pain and swelling; Enhances metabolic homeostasis; Lightens skin and reduce hyperpigmentation; Suppresses appetite; Enhance digestive health; and Promotes bone health [32]; Reduces the absorption of glucose by potently blocking alpha-glycosidases [33].
Cinnamonum verum (Cinnamon) Bark Extract	Cinnamaldehyde, Cinnamic acid; Linalool; eugenol; Polyphenols (catechin and epicatechin); Coumarin; Cinnamyl acetate; and diverse Terpene hydrocarbons.	Offers potent antioxidant and anti-inflammatory benefits; Enhances insulin sensitization; Lowers blood glucose; Anti-diabetic; Reduces blood pressure and cholesterol level; Boosts cognitive function; Improves digestive health; Anti-bacterial; Anti-fungal; Enhances immune competence [4, 35, 36].
Gymnema sylvestre Extract	Triterpene saponins including gymnemic acids; gymnemarins, gymnemasaponins; organic acids; flavonoids; anthraquinones; amino acids; and phytosterols	Exhibits potent antioxidant and anti-inflammatory properties; Regulates blood sugar level; Enhances weight loss; Boosts cardiovascular health; Lowers LDL cholesterol and triglyceride levels; and reduces the craving for sweet foods [37, 38].
Cissus sicyoides Leaf Extract (Insulina)	Flavonoids (quercetin-3-α-rhamnoside and kaempferol-3-α-rhamnoside); Steroids; Coumarins; Stilbenes; Triterpenes; Tannins	Exhibits potent anti-diabetic and anti-inflammatory benefits; Alleviates pain; Regulates blood sugar; Improves bone health; Also acts as anti-bacterial; antioxidant; and Gastro-protectant [39].
Alpha-Lipoic Acid	A potent mitochondrial antioxidant; Boosts energy production.	Acts as a potent free radical scavenger; Boosts insulin sensitization; Reduces blood sugar level; Lowers the symptoms of diabetic neuropathy including numbness, pain, and burning sensation; and helps enzymes in converting carbohydrates into energy [40].
Phellodendron amurense Bark Extract (Berberine HCl)	Bioactive alkaloid. Activates AMP kinase to increase ATP production	Potent antioxidant, anti-inflammatory, Boosts metabolic homeostasis; [41]. Improves insulin sensitivity, reduces liver glucose production and improves cellular glucose uptake [42-44].

Cissus quadrangularis Extract	Triterpenoids (alpha amyrin, beta amyrin, friedelin); Flavonoids (quercetin, daidzein, genistein); Phytosterols (beta-sitosterol); Saponins; Stilbenes (resveratrol, *quadrangularin A*, and piceatannol); IriDOIds (6-O-[3-dimethoxy]-trans-cinnamoyl catalpol and picroside); Vitamin C; Tannins; and Calcium.	Possesses potent antioxidant and anti-inflammatory benefits; Promotes bone growth and healing; Reduces body weight and body fat by appetite suppression and enhancing metabolic homeostasis; Improves digestive health by reducing bloating, gas, and constipation; Improves blood sugar regulation and reduces cholesterol; Enhances muscle growth and wound healing [45].
Lagerstroemia speciosa (Banaba) Leaf Extract	Triterpenes including corosolic acid and asiatic acid; Ellagic acid; Flavonoids (quercetin and isoquercitrin); Tannins, Glycosides; Phenolic acids; Steroids; Amino acids; and Carbohydrates	Traditionally recommended to combat diabetes mellitus; Lower blood glucose levels; Exhibit antidiabetic, antioxidant, anti-inflammatory, and anti-obesity benefits [46].
Fish Oil	Omega-3 fatty acid supplement enriched in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).	Decreases triglycerides and LDL cholesterol; Facilitates management if blood pressure: Reduces the risk of heart disease and stroke; Boosts cognitive function and memory; Prevents against age-related cognitive decline; Lower the risk of Alzheimer's disease; Mitigate inflammation and arthritic pain; Enhance joint mobility; Prevents age-related macular degeneration (AMD); and Lower the risk of dry eye syndrome [47, 48].

Ethical Approval: A stringent inclusion and exclusion criteria procedure was followed for subject recruitment procedure. The clinical practices and procedures, and methodologies of this randomized, double-blind, placebo-controlled study strictly followed the protocol [Protocol NH/231201/GC/DM dated Jan 25, 2024; Ref: IRB Proposal "A randomized, double-blind, placebo-controlled study to assess the effect of the Investigational Product (IP) on metabolic health in individuals with prediabetes or diabetes mellitus"] approved by the Institutional/Independent Ethics Committee (IEC) and followed all applicable laws and regulations, including but not limited to current ICH-Good Clinical Practices (GCP), New Drugs and Clinical Trials Rules, 2019, and the National Ethical Guidelines for Biomedical and Health Research involving Human Participants, Indian Council of Medical Research, 2017. Patient confidentiality was strictly maintained throughout the study. The study was registered with the NIH ClinicalTrials.gov (Identifier: NCT06496893) and Clinical Trials Registry India (Registration Number: CTRI/2024/07/071682).

Compliance Monitoring: The investigator instructed the research participants regarding the proper use of the IP and advised the participants about their obligations and responsibilities. To ensure that the research participant is taking the IP properly, records of dispensed and returned medication were maintained by counting the number of soft gel in the bottle. Also, individual diaries were provided to all participants for ensuring compliance. The participants were asked to fill their daily activities, food intake and supplement intake in their diary. Any concomitant medication taken by the study participants were recorded in the SD and e-CRF. At least 90% compliance was mandated for the research participants during the treatment period. Participants conforming to above conditions were included in the per-protocol population for analysis.

Allocation concealment: To avoid selection bias in this placebo-controlled randomized investigation, allocation concealment was conducted to the study groups from those responsible for the assessment of the subjects entering the trial. Six investigational product bottles were packed for each research participant in each arm in HDPE bottle, with the research participant ID according to the randomization schedule. Each bottle contained 70 soft gels for Day 0, 30 and 60 (as per the investigator's instructions). The label of each bottle had participant ID, visit day, batch number of the product, date of manufacturing and expiry, and direction of use.

To preserve the blinding, Glucocil® and placebo soft gel were matched for size, shape, color, and texture. The soft gels were packed identically in terms of size, color, and labelling. The blinding was done by the CRO (Vedic Lifesciences). The investigator, site, and CRO study team, and the participants were blinded to the investigational product allocation. Each clinical study site was assigned a specific identification number.

Recruitment of Study Participants: All subjects were recruited from the outpatient department/existing database following a stringent IRB-approved inclusion and exclusion criteria until the planned number of participants was achieved (Table 1). All recruited subjects were thoroughly examined and critically screened and evaluated for this clinical study. A total of 202 participants were screened, of whom 98 (48.5%) were screen failures or discontinued during screening. Forty-one subjects were pre-diabetics, who were randomized into two groups (Glucocil® = 22; placebo = 19). The remaining 63 subjects were type II diabetics, who were used for another study.

One placebo participant in the pre-diabetic group discontinued on day 0 and another placebo participant progressed from prediabetes to diabetes by the end of the study. Both participants were excluded from the analysis, yielding a full analysis set (FAS) of 39 pre-diabetic participants (Glucocil® n=22, placebo n=17) (Figure 1). Two participants with clinically discordant biomarker profiles were excluded, resulting in a modified FAS (mFAS) of 37 participants (Glucocil® n=21, placebo n=16) (Figure 1).

As a double-blind study, stratified block randomization was conducted using the StatsDirect software version 3.1.17 to avoid bias with respect to various strata of the data including age, sex, gender etc., whereas the allocation of participants was done as per the randomization chart. The randomization chart was then secured, saved and maintained in the respective study folder with limited access. The recruited subjects were asked not to alter their daily physical activities. Table 3 exhibits the age, height, body weight, body mass index (BMI), waist circumference and blood pressure of all the recruited pre-diabetic subjects in the placebo and Glucocil® groups. Subjects were advised to consume either 4,800 mg/day of placebo (soybean oil; 1,200 mg/soft gel) or Glucocil® soft gels (1,200 mg/soft gel) over a period of 90 consecutive days. Both Glucocil® and placebo groups were instructed to consume two soft gels (1,200 mg/soft gel) with breakfast and two soft gels (1,200 mg/soft gel) with dinner per day. Thus, the daily dose was 4,800 mg/day for both placebo and Glucocil® groups. All placebo and Glucocil® subjects were asked to maintain daily diaries and get it regularly endorsed by the study coordinators. Adverse event monitoring was strictly ascertained.as secured, saved, and maintained in the respective study folder with limited access.

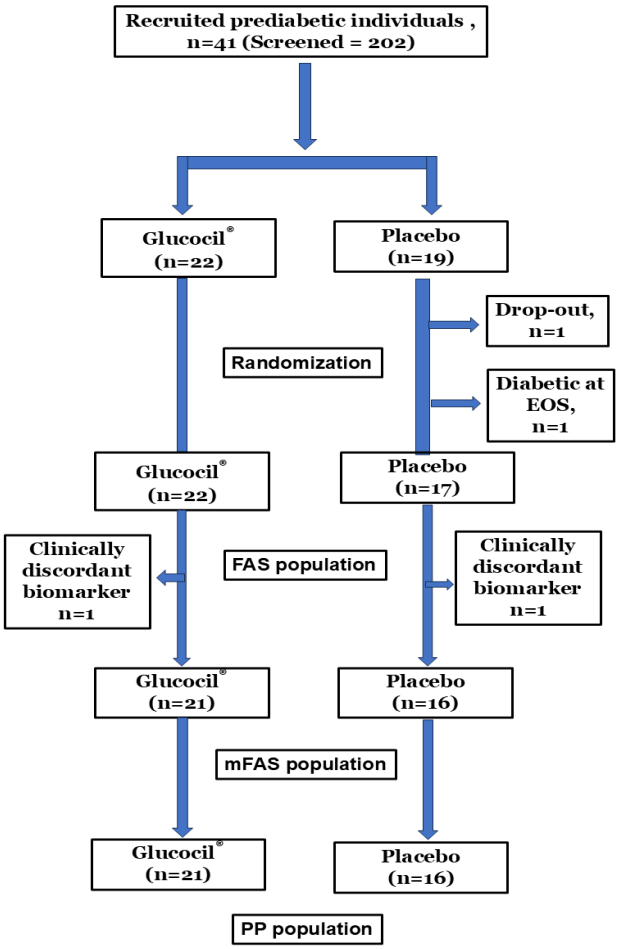


Figure 1. Consort diagram of the study: A total of 41 prediabetic individuals were distributed into Glucocil® (n=22) and Placebo (n =19) groups out of which 37 (Glucocil®, n=21 and Placebo, n =16) completed the study.

Investigation Discontinuation Clause: The basis for "stopping" of trial or "discontinuation criteria" was that which could have happened only in case of serious adverse events (as outlined in the safety assessments clause).

Concomitant Medication: The prescription medications consumed during the study by the study participants were strictly monitored and recorded on the case report forms (CRFs). Consumed medications included concomitant prescription medications, over-the-counter medications (OTC) and non-prescription medications. The investigators prohibited several medications during the study, while the rescue medications were provided to the study participants as and when needed.

Compliance: Study investigators distributed both the placebo and Glucocil® capsules to the enrolled subjects. The investigator instructed the recruited subjects regarding the proper use of the investigational product (IP) and informed the participants of their obligations and responsibilities. To ensure that the research participant was taking the IP properly, records of dispensed and returned medication were maintained by counting the number of soft gels in the bottle. Also, a diary was provided to each participant for ensuring compliance. The participants were asked to fill in the information regarding the IP missed or lost details in the diary. Any concomitant medication taken by the research participant was recorded in the SD and electronic Case Report Form (e-CRF). The research participants with at least 90% compliance during the treatment period and

conforming to above conditions were included in per-protocol population for analysis.

Six IP bottles were packed for each study participant in each arm in HDPE bottle, with the study participant ID according to the randomization schedule (provided by Vedic Lifesciences). Each bottle contained 70 capsules for dispensing on day 0, 30 and 60 of treatment. The bottle label had study participant ID, visit day, batch number of the product, date of manufacturing and expiry, and direction of use. The IP was advised to maintain at room temperature in a cool and dark place protected from direct sunlight. Allocation and distribution of the IP was done by the site staff only. IP accountability log was routinely maintained, and every single entry was saved separately.

Table 2. Inclusion and Exclusion Criteria

Inclusion Criteria
1. Males and females of age ≥ 30 and ≤ 70 years
2. Body mass index (BMI): 25 – 35 kg/m^2
3. Waist circumference >40 inches (male) or 35 inches (female)
4. Subjects newly diagnosed with prediabetes as assessed by FBG: 100-125 mg/dL
5. Triglycerides ≥ 101 and ≤ 299 mg/dL and/or Low-Density Lipoprotein (LDL) ≥ 130 and ≤ 189 mg/dL
6. Individuals have non vegetarian diet for at least 2 days in a week.
7. Non-smoker
8. Agree not to change their physical activity
9. Complete all study-related questionnaires and complete all clinical study visits.
10. Provide voluntary, written informed consent to participate in the study.
Exclusion Criteria
1. Vegetarian Subjects
2. Subjects with Type 1 diabetes mellitus
3. Subjects with Type 2 diabetes mellitus on medication
4. Subjects with any other endocrine disorder
5. Subjects taking diuretics or thyroid supplements.
6. Individuals on lipid-lowering therapies
7. Individuals with uncontrolled hypertension as assessed by systolic over diastolic blood pressure (≥ 140/90 mmHg)
8. Individuals on antihypertensive medication
9. Individuals with cardiac arrhythmia, impaired hepatic or renal function
10. Individuals have heart failure, coronary artery disease (CAD), hyperthyroidism, hypothyroidism, cancer or mental disease or any other serious disease requiring active treatment
11. History of malignancy or stroke
12. Chronic alcoholism
13. Individuals taking concomitant medication known to alter blood sugar
14. Individuals have any other herbal supplements
15. Any condition or abnormality that would compromise the safety of the individuals or the quality of the study data.
16. Use of another investigational product within 3 months of the screening visit
17. Lactating women, pregnant or planning to be pregnant or taking oral contraceptive(s)

Assessment of fasting blood glucose: Fasting plasma glucose levels (mg/dL) were assessed at 0, 30, 60 and 90 days of treatment using kits from the authorized distributor of Roche Cobas, Roche Healthcare (Basel, Switzerland).

Assessment of Oral Glucose Tolerance Test (OGTT): OGTT was carried out at the 0^{th} day (time of recruitment) and on the 90^{th} day of treatment as per standard protocol. Briefly, plasma glucose levels were measured at the baseline (after 8-12 h of fasting) and then again after 2 h of consumption of 75 gm glucose solution immediately after baseline measurement.

Estimation of glycosylated hemoglobin (HbA1c) levels: HbA1c levels were determined at 0, and 90 days of treatment using kits manufactured by Shenzhen Lifotronic Technology (Shenzhen, China).

Estimation of fasting insulin levels: Insulin levels were determined at 0, and 90 days of treatment using kits manufactured by Roche Cobas, Roche Healthcare (Basel, Switzerland).

Monitoring the adverse events: All recruited subjects were instructed to record all types of adverse events in their daily diary during this study. Moreover, lipid profile, liver function tests including serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT), bilirubin, albumin, and total protein were estimated in both placebo and Glucocil® groups at the beginning and completion of the study. During each of their visits, study participants were critically questioned if they had experienced any untoward situation/problems or difficulties. Overall, adverse event reporting was strictly enforced.

Statistical Analysis: Data were presented as mean + standard deviation (S.D.). Normal distribution of the data was assessed by Shapiro-Wilk Test to negate the possibility of any hidden biasness. For inferential tests, p-value <0.05 and 95% confidence intervals (CI) were considered for statistical significance and two-tailed hypothesis was performed in each case to ascertain whether Glucocil® was significantly better or worse than the placebo. A Welch's t-test was conducted to assess the difference between treatment and placebo groups owing to their unequal sample sizes. The least-square means, difference estimates, and p-values were calculated by using ANCOVA with treatment as factor and Baseline value as covariate. p-value was calculated using student's t-test (T) for continuous variables and Chi Square (C) test for Categorical Variables. Percentages were calculated using respective column header count as denominator.

RESULTS

The study investigated the effect of Glucocil®, a bioengineered concoction made from 14 nutrition ingredients, in 37 randomized individuals with 21 being in the treatment group and the rest 16 in the placebo group. There was no significant difference or bias in demographic or anthropometric attributes indicating that both the treatment arms were free from any bias at the start of the treatment (Table 3).

Table 3. Age, height, body weight, body mass index (BMI), waist circumference and blood pressure of all the recruited pre-diabetic subjects

Data	Glucocil®	Placebo	p-value
Age (yrs)	45.04 ± 11.29	45.88 ± 11.22	0.7023
Height (meters)	1.61 ± 0.10	1.62 ± 0.08	0.7222
Weight (kg)	74.95 ± 9.97	77.66 ± 11.45	0.2021
BMI (kg/m^2) (Female)	29.11 ± 1.84	30.11 ± 2.86	0.3209
BMI (kg/m^2) (Male)	28.78 ± 2.32	29.52 ± 2.92	0.2172
Average waist circumference (cm) (Female)	99.70 ± 6.68	100.60 ± 7.65	0.7552
Average waist circumference (cm) (Male)	107.11 ± 4.14	107.97 ± 4.76	0.3989
Waist/Height Ratio (Female)	0.6572 ± 0.0407	0.6712 ± 0.0508	0.4537
Waist/Height Ratio (Male)	0.6504 ± 0.0366	0.6559 ± 0.0308	0.4847
SBP (mmHg)	121.68 ± 4.22	123.89 ± 3.70	0.0814
DBP (mmHg)	77.82 ± 4.40	79.68 ± 3.35	0.1323
Pulse rate (/min)	79.18 ± 5.60	78.53 ± 5.31	0.7028

Effect of Glucocil® on 2-hour OGTT plasma glucose: To assess the effect of Glucocil® on management of postprandial blood sugar levels in the recruited prediabetic individuals, Oral Glucose Tolerance Test (OGTT) was employed to determine the post-prandial blood sugar levels (Figure 2). The baseline 2-hour plasma glucose levels were similar between the Glucocil® group (165.26 mg/dL±41.39) and the placebo group (162.75 mg/dL±21.43), with no significant difference between groups (p = 0.8194). At Day 90, the mean levels decreased to 141.16 mg/dL(±19.09) in the Glucocil® group and 146.00 (± 33.42) mg/dL in the placebo group, again showing no significant difference between groups (p = 0.6126). However, within-group analysis showed a significant reduction in blood glucose from baseline in the Glucocil® group (p = 0.0131), while the reduction in the placebo group was not statistically significant (p = 0.0549).

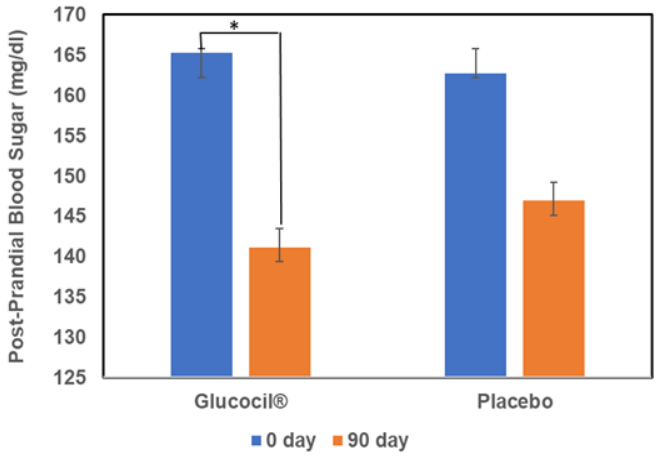


Figure 2: Effect of Glucocil® on post-prandial blood glucose: PP blood glucose level was significantly reduced in the Glucocil® group after 90 days of treatment. * Indicate significant reduction in blood glucose level (p = 0.0131).

Effect of Glucocil® on Glycated Hemoglobin: The glycated hemoglobin (HbA1C) content gives a good picture of the long-term average blood sugar of a person in terms of percentage of hemoglobin which has been glycated by glucose [49]. A value of 6.5 is recognized as a cut-off point over which the patient is diagnosed as diabetic. At baseline, the mean HbA1c was slightly higher in the Glucocil® group (6.44±0.28) compared to Placebo (6.22±0.38), but this difference was not statistically significant (p = 0.0684). At Day 90, HbA1c decreased to 5.80 (±0.52) (Glucocil®) and 6.06 (±0.74) (placebo) (p=0.2640). Within-group reduction was significant for Glucocil® (p=0.0002) but not for placebo (p=0.2930) (Figure 3). The mean HbA1c change was greater with Glucocil® (−0.64) than placebo (−0.17), with a significant between-group difference (p=0.0301).

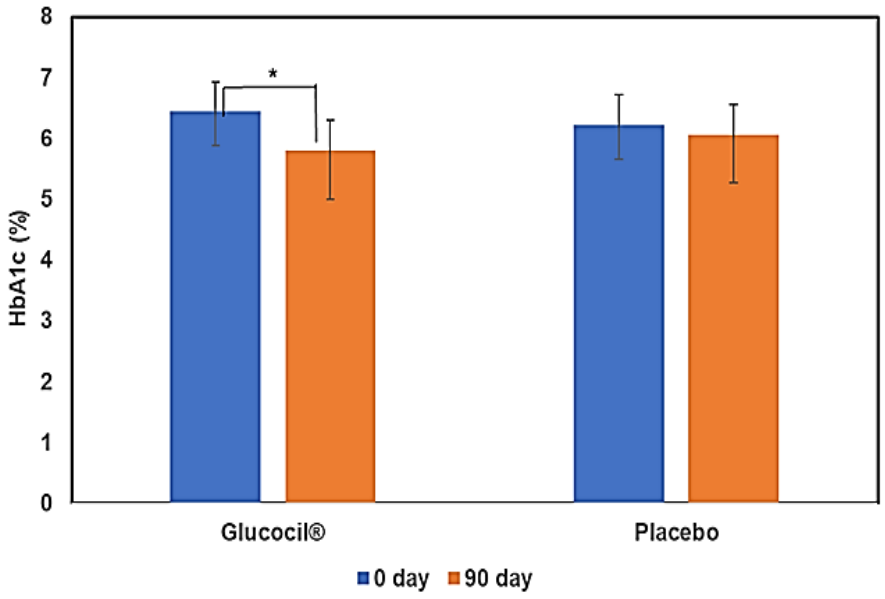


Figure 3: Effect of Glucocil® on glycated hemoglobin (HbA1c). Administration of Glucocil® over a period of 90 days resulted in significant reduction in HbA1c levels. * Indicates significant reduction in blood glucose level (p=0.0002).

Effect of Glucocil® on fasting insulin: Fasting insulin serves as an indirect indication of the developing of insulin resistance in the body [50] which could lead to Type 2 diabetes [51]. At baseline, the mean fasting insulin levels were similar between Glucocil® (28.39±21.80) and placebo (29.21±35.32) groups (p = 0.9359) (Figure 4). Across follow-up visits at day 30 and day 90, there were no significant differences between groups (p = 0.9914 and p=0.9027 respectively for day 30 and day 90). At Day 60, the Glucocil® group showed a lower mean insulin level (15.09±9.84) as compared to the placebo (23.46±18.46), Within-group analysis showed a significant reduction from baseline at Day 60 in the Glucocil® group (p = 0.0324), while the placebo group did not show significant change at any visit. The results suggested that although Glucocil® was able to reduce the levels of fasting insulin initially over the first two months, subsequently, there was a possible acclimatization or tolerance resulting in subsequent increase in fasting insulin again.

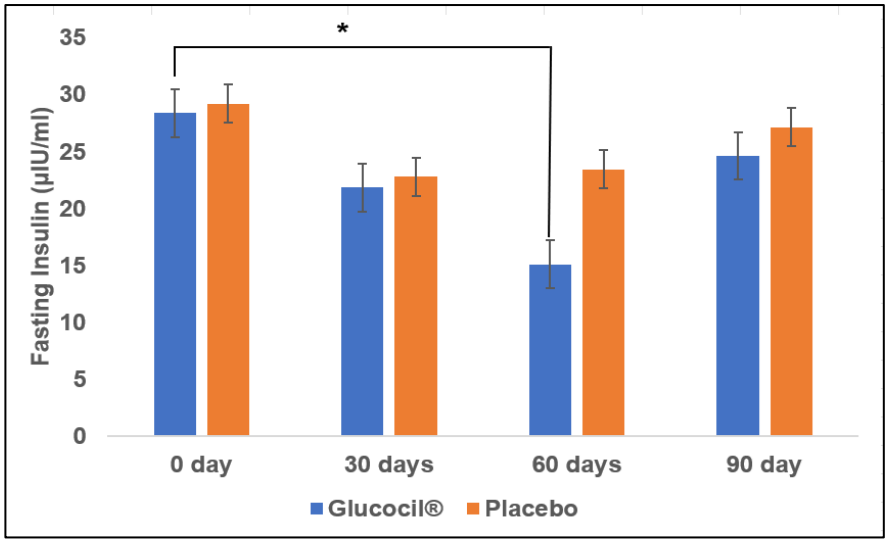


Figure 4: Effect of Glucocil® on fasting insulin levels. Fasting insulin levels were significantly reduced in the Glucocil® group at the end of 60 days. * Indicates significant reduction in fasting insulin level (p = 0.0324).

Effect of Glucocil® on fasting glucose levels: To further substantiate the role of Glucocil® in the management of blood glucose level, fasting blood glucose levels were also investigated subsequently at designated intervals (Figure 5). At baseline, mean fasting blood glucose (FBG) levels were similar between the Glucocil® group (111.90 mg/dL±41.78) and the placebo group (113.44 mg/dL±25.53; p=0.8913). By day 30, FBG went down by 14.19 mg/dL in the Glucocil® group and by 4.88 mg/dL in the placebo group, though neither within-group (p = 0.1850 and p = 0.5499, respectively) nor between-group (p=0.4802) differences were statistically significant. At the end of 60 days, Glucocil® group continued to show a mean reduction by 13.52 mg/dL, whereas that in case of the placebo group went up by 10.56 mg/dL. At the end of the study (Day 90), both groups demonstrated modest reductions from baseline by 9.71 mg/dL for Glucocil® and 7.75 mg/dL for placebo albeit without any statistical significance.

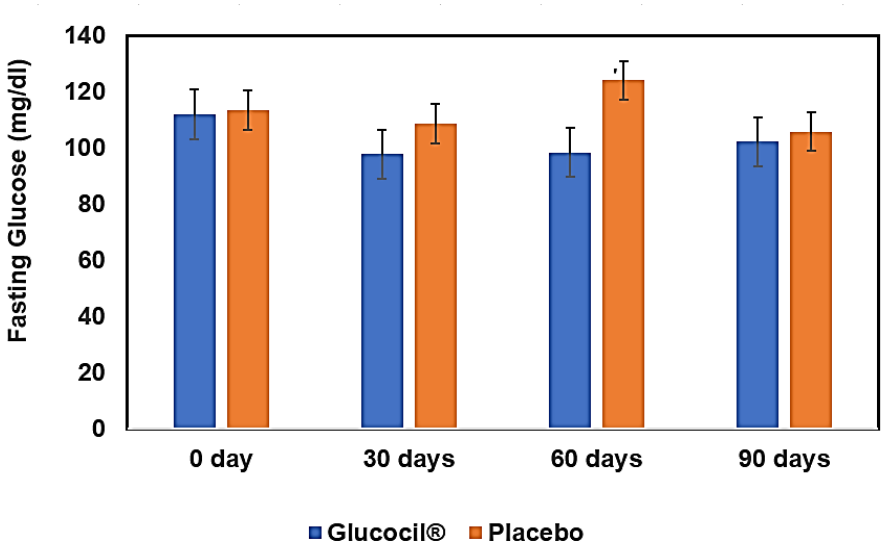


Figure 5: Effect of Glucocil® on fasting glucose levels**:** No significant difference in fasting glucose levels was noted in the Glucocil® group at the end of 90 days of treatment.

Effect of Glucocil® on change in body weight: To assess the effect of Glucocil® on holistic body physiology, body weight of the individuals at the end of the study period was determined. At baseline, the mean body weight was 77.43 kg (±10.62) in the Glucocil® group and 82.45 kg (±12.21) in the placebo group, with no significant difference between groups (p=0.2002). At Day 90, the mean body weight decreased to 76.22 kg (± 10.45) in the Glucocil® group and 80.78 kg (± 12.19) in the placebo group; the between-group difference remained non-significant (p=0.2407). No significant difference was also observed between treatments. Both groups showed statistically significant within-group weight reductions at all follow-up visits, with Glucocil® demonstrating a reduction of -0.27 kg at Day 30 (p=0.0563), -0.81 kg at Day 60 (p=0.0025), and -1.55 kg at Day 90 (p<0.0001). The placebo group also showed reductions of -0.64 kg at Day 30 (p=0.0642), -1.28 kg at Day 60 (p=0.0037), and -2.05 kg at Day 90 (p=0.0005). Percent weight change followed a similar pattern, with no significant differences between groups at any visit (e.g., -1.55% vs. -2.05% at Day 90, p=0.3516), but both groups had significant within-group percent reductions over time. Overall, weight reductions occurred in both groups, with no statistically significant advantage observed for Glucocil® over placebo.

Assessment of anthropometric index in presence and absence of Glucocil®: Overall, health status of prediabetic individuals was also assessed by anthropometric measurements. At baseline, the mean waist-to-height ratio was similar between the Glucocil® group (0.6393 ± 0.0278) and the placebo group (0.6472 ± 0.0307), with no significant difference (p=0.4224). By the end of the study (Day 90), both groups showed a modest reduction: The change from baseline to Day 90 was -0.0046 (±0.0042) in the Glucocil® group and -0.0057 (±0.0064) in the placebo group, with a non-significant between-group difference (p=0.5511). However, within-group analysis showed statistically significant reductions from baseline at Day 60 and Day 90 in both Glucocil® (p=0.0080 and p=0.0001, respectively) and placebo groups (p=0.0094 and p=0.0027, respectively).

Although both Glucocil® and placebo groups exhibited statistically significant reductions in waist-to-height ratio within groups, the between-group comparison showed no meaningful difference at any time point, indicating that Glucocil® did not demonstrate a superior effect over placebo in improving this anthropometric index. Therefore, no conclusive advantageous effect of Glucocil® over placebo was demonstrated in terms of the anthropometric index.

Assessment of changes in lipid profile induced by Glucocil®: As a part of evaluating the safety assessment vs holistic health benefits imparted by consumption of Glucocil®, lipid profile of the recruited patients was determined after the entire study of 90 days (Figure 6). Total cholesterol decreased modestly in both groups by Day 90, with no statistically significant differences between groups or within groups over time. Triglyceride levels remained relatively stable with minimal change in both groups, and no significant differences were observed. HDL cholesterol showed an increase in the Glucocil® group and a slight decrease in the placebo group by Day 90; however, these changes were not statistically significant. LDL cholesterol decreased in both groups, with a larger but not statistically significant reduction in the Glucocil® group compared to placebo. Overall, while trends toward improvements in lipid parameters were observed, especially reductions in total cholesterol and LDL with Glucocil®, none of the changes reached statistical significance when comparing between groups or relative to baseline.

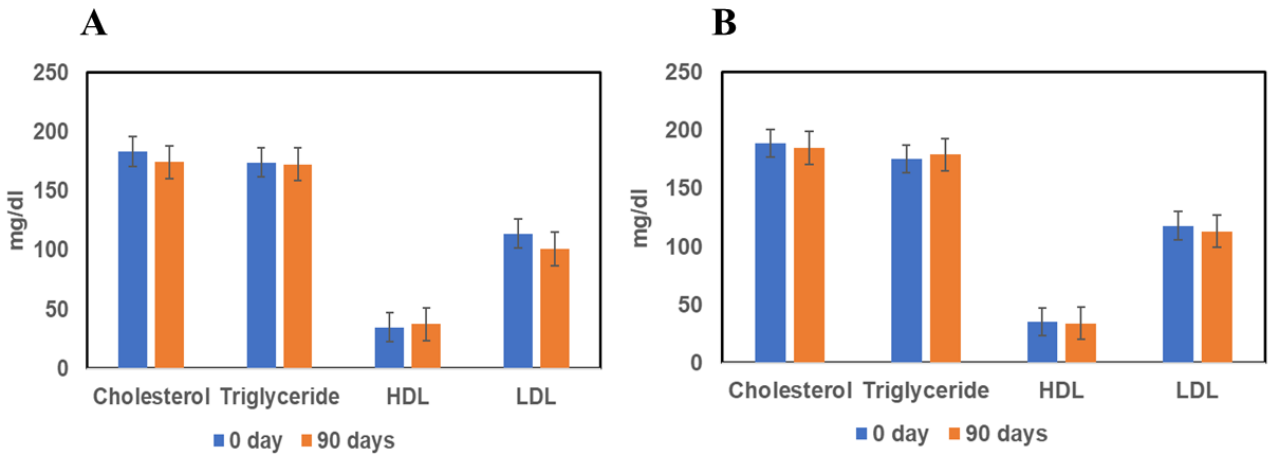


Figure 6: Effect of Glucocil® in lipid profile: No significant change Cholesterol, triglyceride, HDL and LDL levels were assessed in A) Glucocil® and B) Placebo groups at the end of 90 days of treatment.

Assessment of Safety of Glucocil®: Determination of cardiovascular parameters: Safety assessment of Glucocil® was conducted in terms of vital signs evaluation. Pulse rate, systolic and diastolic blood pressure were evaluated concomitantly at the base line and at the end of 30 days, 60 days and 90 days. There was no appreciable change in any of the three parameters in Glucocil® or placebo groups during the entire study period. Overall, vital signs remained consistent and within normal ranges, indicating no adverse effects related to Glucocil® treatment on cardiovascular parameters (Figure 7).

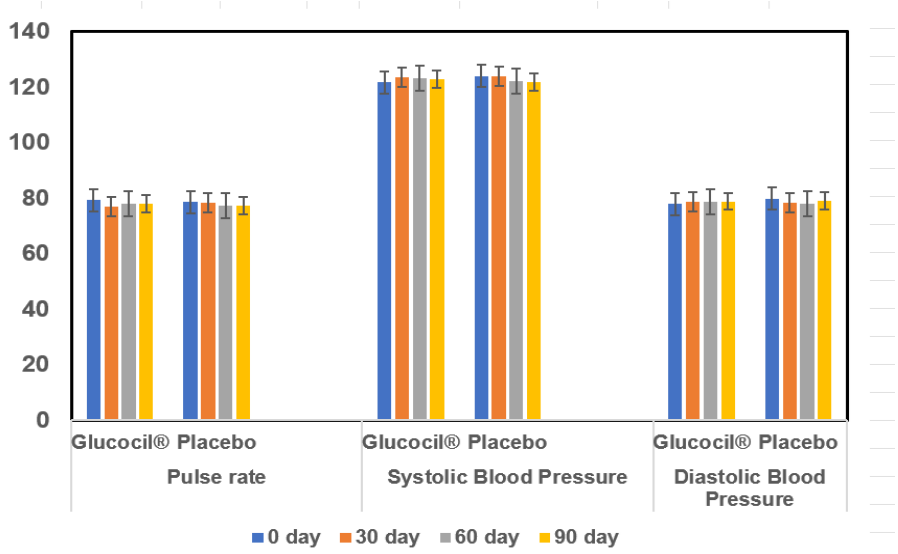


Figure 7: Effect of Glucocil® on cardiovascular parameters. Safety assessment of Glucocil® was carried out with respect to cardiovascular. No significant change was noticed either in Pulse rate, Systolic Blood Pressure or Diastolic Blood Pressure

Assessment of safety of Glucocil®: Evaluation of liver function parameters: Liver function was evaluated based on the four marker enzymes Serum glutamic pyruvic transaminase (SGPT), a.k.a. Alanine aminotransferase, serum glutamic-oxaloacetic transaminase (SGOT), a.k.a. Aspartate transaminase, Alkaline Phosphatase (ALP), and

Gamma-Glutamyl Transferase (GGT) [52]. Additionally, the levels of total serum protein and albumin were also determined as additional reliable indicators of liver function test. Total bilirubin levels were also ascertained. (Figure 8). Across all liver function markers, no statistically significant differences were observed between Glucocil® and placebo groups. Most parameters remained stable or changed minimally from baseline. While AST showed a non-significant favorable trend with Glucocil®, the overall data pointed towards the fact that Glucocil® was safe also for hepatic system

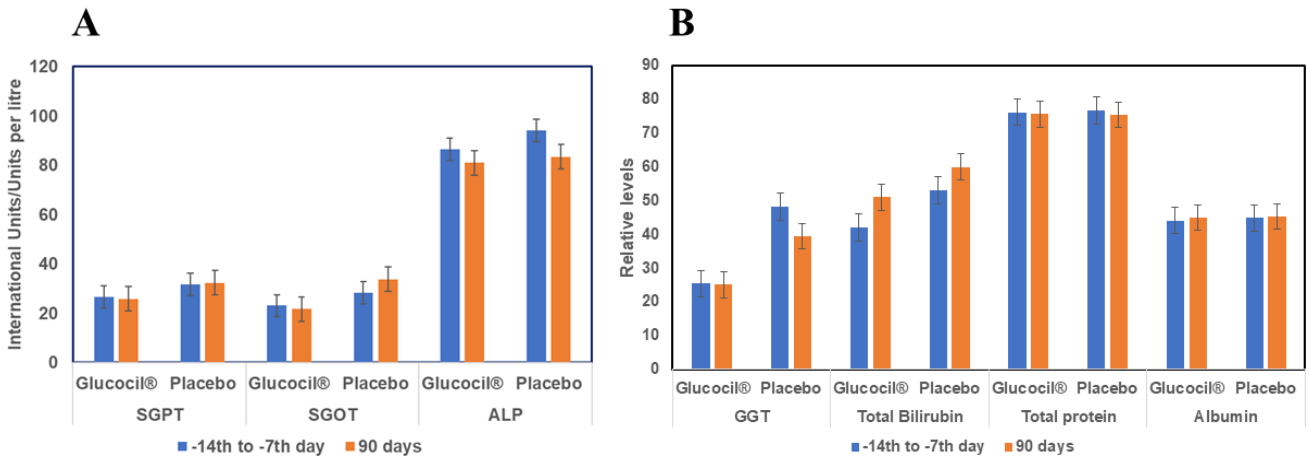


Figure 8: Effect of Glucocil® on liver function parameters. Safety assessment of Glucocil® was carried out with respect to liver function test. No significant change was noticed either in SGPT, SGOT or ALP levels (8A) or GGT, total bilirubin, total protein and albumin levels (8B).

DISCUSSION

In this randomized, double blind, placebo-controlled study, Glucocil® was found to produce a significantly greater reduction in HbA1c than placebo in the studied prediabetic population (−0.64 vs −0.17; p=0.0301). This was accompanied by a significant within-group reduction in 2-hour OGTT glucose in the Glucocil® arm (p=0.0131), although between-group differences for OGTT outcomes were not statistically significant. Given prior evidence that postprandial glycemia contributes disproportionately to HbA1c at lower HbA1c levels [2], the observed reduction in 2-hour OGTT glucose offers a plausible physiologic explanation for the HbA1c improvement at Day 90 despite the absence of a significant change in fasting blood glucose. One placebo participant progressed to diabetes by end of study, an observation that is clinically relevant but not interpretable as a treatment effect given the sample size.

The observed glycemic changes in the Glucocil® group was possibly caused by an increase in insulin sensitivity, since there was a parallel decline in fasting insulin. However, fasting insulin and fasting blood glucose were measured in intervals of 30 days and thrice during the entire study period. The drop in both the parameters was more significant till 60 days (2nd investigation) but increased subsequently at the end of the study period. This may be attributed to a gradual tolerance or acclimatization of the body to one or more of the antidiabetic agents present in the formulation. In a more likely scenario, decline in efficiency of insulin sensitizers over time may be indicative of the progression of T2DM with lesser production of insulin by the β cells [53]. To gain further mechanistic insights into this process, the respective bioactives present in the

constituents and their individual and synergistic roles must be identified. The antidiabetic compounds present in mulberry leaves are chiefly 1-deoxy nojirimycin and flavonoids [54]. 1-Deoxy nojirimycin is a competitive inhibitor of alpha-glucosidase which slows down carbohydrate metabolism and reduces absorption of glucose thus controlling the rise in blood sugar levels [55]. Cinnamon also contains polyphenols such as cinnamaldehyde and flavonoids such as proanthocyanidins [56] which act by modulating the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathway and the AMP activated Protein Kinase (AMPK) pathway, which improves insulin sensitivity and enhanced glucose uptake from bloodstream [57]. *Gymnema sylvestre* is a rich source of gymnemic acid, a triterpene based saponin capable of reducing intestinal glucose absorption [58] and increasing insulin sensitivity possibly through peroxisome proliferator-activated receptor δ (PPARδ)- and nuclear factor κB (NFκB)-mediated signalling pathways [59]. *Cissus sicyoides*, also known as insulina plant contains a rich source of flavonoids and tannins such as the quercetin 3-rhamnoside, kaempferol 3-rhamnoside, resveratrol, beta-sitosterol, coumarin glycoside and tyramine [60]. Most of these compounds resemble biguanide drugs such as metformin. These drugs arrest liver gluconeogenesis resulting from metabolic abnormalities like dyslipidaemia. and other related metabolic abnormalities and thus prevent the rise in free glucose. 61. Berberine and Phellodendrine are the two chief isoquinoline alkaloids found in abundance in the barks of *Phellodendron amurense* [62] which exert their antidiabetic function by promoting insulin sensitivity and improving lipid metabolism [63]. This was also reflected in the Glucocil® group as HDL cholesterol was increased significantly as compared to the placebo group. Banaba leaf contains corosolic acid and ellagitanins which assist in lowering blood sugar levels through multiple mechanisms [64]. Corosolic acid is a terpenoid which promotes glucose uptake by cells, increases insulin sensitivity and prevents hydrolysis of starch whereas ellagitannins possess insulin mimetic effects [65].

Other supplements fortified in Glucocil® included alpha-lipoic acid which acts as a strong antioxidant by promoting Nrf-2 mediated antioxidant gene expression. In addition, it is an efficient quencher of reactive oxygen species and can also reduce oxidized forms of vitamin C, vitamin E, and glutathione [66]. Fish oil is enriched in polyunsaturated fatty acids which are effective anti-inflammatory agents [67]. Cumulatively, the formulation demonstrated potential to cater for its original objective, that is reduction of high glycemic index of prediabetic individuals subsequent arrest from proceeding into a diabetic stage. Although there was a notable reduction in HbA1c levels in this pilot study, the trends in fasting glucose and fasting insulin together with the modest cohort size are obvious limitations of the study. Better insights are expected from extended trials beyond 90 days with a bigger sample size, to be conducted soon in future.

CONCLUSION

Owing to the increasing long term safety concerns arising out of the use of conventional antidiabetics, the necessity to explore the combinatorial potential of phytotherapeutic molecules has been the need of the hour. The current pilot study conducted on a modest cohort size of 21 prediabetic individuals reported the effect of a newly developed dietary supplement, Glucocil®, fortified with the goodness of 14 assorted natural ingredients, on adults with prediabetes. Although the mode of action of the individual components present in the formulation are grossly known, their synergistic potential has not been reported till date to the best of our knowledge. Although the initial results, especially in terms of reduction of HbA1c and safety assessment are

encouraging, more robust and extended trials coupled with parallel mechanistic explorations on diabetic animal models and cell lines needs to be carried out.

List of Abbreviations: AMD: Age-related macular degeneration; AMPK**:** Adenosine monophosphate-a activated protein kinase; BMI: Body mass index; CHD: Coronary heart disease; CVD: Cardiovascular disease; DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acid; HbA1c: GCP: Good clinical practices; HDPE: High-density polyethylene; Hemoglobin A1c or glycated hemoglobin; IEC: Institutional/Independent ethics committee; IP: Investigational product; IRB: Institutional review board; NFκB: Nuclear factor κB; OGTT: Oral glucose tolerance test; PI3K/Akt: Phosphoinositide 3-kinase/Protein kinase B signaling pathway; PPARδ: Peroxisome proliferator-activated receptor δ; PUFA: Polyunsaturated fatty acids; T2DM: Type 2 diabetes mellitus

Authors' Contributions: AB, SK, SR, and esteemed Vedic Lifesciences research team designed the clinical study protocol, which was critically reviewed and approved by LZ, SC, MH and DB, and esteemed Vedic Lifesciences research team exclusively performed the clinical study and data analysis independently. LZ, AB, SK, SR, SC, MH and DB drafted and approved the manuscript. All the authors critically reviewed, agreed and submitted the manuscript to FFHD.

Competing interests: LZ is an employee of Neuliven Health. Other authors declare no conflict of interest. The clinical trial was conducted at Vedic Lifesciences, an independent contract research lab specializing in natural products research. The funder had no role in the design of the study; in the collection, analyses, audit, or interpretation of data.

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Institutional Review Board Statement: The IRB Proposal "A randomized, double-blind, placebo-controlled study to assess the effect of the Investigational Product (IP) on metabolic health in individuals with prediabetes or diabetes mellitus"] approved by the Institutional/Independent Ethics Committee (IEC) and followed all applicable laws and regulations, including but not limited to current ICH-Good Clinical Practices (GCP), New Drugs and Clinical Trials Rules, 2019, and the National Ethical Guidelines for Biomedical and Health Research involving Human Participants, Indian Council of Medical Research, 2017. The study was registered with the NIH ClinicalTrials.gov (Identifier: NCT06496893) and Clinical Trials Registry India (Registration Number-CTRI/2024/07/071682).

Informed Consent Statement: All subjects agreed and duly signed the written informed consent form to participate in the study.

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