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A randomized, double-blind, parallel-arm clinical trial to assess the bioavailable efficacy of *Lipokon™ Berberine* and *Berberine* extract in patients with type 2 diabetes mellitus.

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Abstract

Background: Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and hyperglycemia, leading to various complications affecting organ systems. Berberine, a plant-derived alkaloid, has shown promising effects in improving glycemic control and insulin sensitivity. This Phase 2 clinical trial evaluated the safety and efficacy of **Lipokon™ Berberine** and Berberine extract as an adjunct to oral hypoglycemic agents (OHAs).

Methods: In this double-blind, parallel-arm clinical trial, participants were randomized equally to receive the berberine extract. Primary endpoints included fasting plasma glucose (FPG), post-meal plasma glucose (PPG), HbA1c, fasting insulin, and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR). Secondary endpoints included lipid profile, Metabolic Syndrome Severity Z-score (MetS-Z), anthropometric parameters, and diabetes-related quality of life score (DQOL). Assessments included adverse events (AEs), vital signs, tolerability, and compliance.

Result: Both the treatment groups showed significant reductions in FPG, PPG, and HbA1c levels. Decrease in levels of HOMA-IR was comparable in Standard Berberine and Lipokon™ Berberine (65.75 % vs 64.45%). Lipid parameters, MetS-Z scores, and anthropometric measures improved in both groups, accompanied by 36-37% improvement in DQOL scores. No serious AEs occurred; all events were mild, self-limiting, and unrelated to the investigational product.

Conclusion: Lipokon™ Berberine demonstrated clinically meaningful improvements in glycemic control, insulin resistance, lipid metabolism, metabolic syndrome severity, and quality of life, with good

safety and tolerability. The formulation may serve as a potential adjuvant to oral hypoglycemic agents (OHA).

Keywords: Type 2 diabetes mellitus; Herbal formulation; Metabolic syndrome, Lipokon™ Berberine

1. Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by elevated blood sugar levels, stemming from impaired insulin secretion, insulin resistance, or both [1]. This condition gives rise to both microvascular and macrovascular complications, including retinopathy, nephropathy, neuropathy, ischemic heart disease, peripheral vascular disease, and cerebrovascular disease, often leading to significant tissue and organ damage [2].

The prevalence of diabetes mellitus, which was 529 million in 2021, is anticipated to rise, with projections suggesting that 1.31 billion people worldwide could be living with diabetes by the year 2050. [3] India ranks the second-highest global prevalence of T2DM, with an estimated 74.2 million cases in 2021, and projections anticipate a substantial rise to 124.9 million by 2045 among adults aged 20–79 years. It is the most common type of diabetes, accounting for more than 90% of all diabetes worldwide [4].

T2DM, often termed the "silent disease," progresses steadily without early symptoms, culminating in severe organ damage. The increasing prevalence is linked to urbanization, lifestyle changes, and shifts in dietary patterns [5]. The risk factors associated with type 2 diabetes, including sleep quantity/quality, smoking, dyslipidemia, hypertension, ethnicity, family history, obesity, and physical inactivity, significantly influence its development [6].

Conventional pharmacological treatments for managing hyperglycemia include the use of various medications either individually or in combination. These include sulfonylureas, which stimulate insulin release from pancreatic cells; biguanides, which decrease glucose production in the liver; PPARγ agonists, which enhance insulin activity; and α-glucosidase inhibitors, which hinder glucose absorption in the intestines [7]. However, limitations such as hypoglycemia, weight gain, and inadequate therapeutic efficacy, liver or kidney disorders. Despite advancements in anti-hyperglycemic agents, optimizing therapy and reducing long-term complications remain significant challenges [7,8].

Adjuvant therapies using medicinal plants and vitamins, advocated by the World Health Organization, present promising avenues for T2DM management. The utilization of such natural compounds has a rich history, with billions worldwide relying on them for metabolic disease treatment. Scientific evidence highlights the efficacy of these adjuncts in regulating blood sugar levels through mechanisms such as enhancing insulin action, protecting against diabetic complications, and exhibiting anti-diabetic properties. Phytochemicals found in medicinal plants encompass a diverse array, including alkaloids, flavonoids, phenols, and terpenoids, with demonstrated anti-diabetic effects.

Berberine, a plant-derived alkaloid, improves glucose control and insulin sensitivity, supporting its role as an adjuvant in type 2 diabetes mellitus (T2DM) [9]. A randomized, double-blind trial evaluated its efficacy and safety alongside oral hypoglycemic agents in T2DM patients. Berberine exhibits low oral bioavailability due to extensive degradation in the gastrointestinal tract. Liposomal encapsulation of

berberine within phospholipid vesicles protects it from enzymatic breakdown, enhances intestinal absorption, and facilitates cellular uptake. This delivery system increases systemic bioavailability, allowing lower doses to achieve therapeutic effects. Liposomal berberine has been shown to effectively support blood glucose regulation, improve insulin sensitivity, and aid in weight management, offering a more reliable and efficient alternative to conventional formulations.

Materials And Methods

Study Design and Setting

This was a randomized, double-blind, parallel-arm clinical trial designed to assess the efficacy and safety of Lipokon ™ Berberine compared with standard Berberine extract in patient with T2DM. The study was conducted at Lokmanya Medical Research Centre and Hospital. Participants were randomly allocated (as per computer-generated randomization list using SPSS software) prepared by qualified statistician. All the investigators or their designated study staff, study participants, sponsors, and study monitors were blinded to the assigned treatment.

Ethical Consideration

The study protocol was approved by the Institutional Ethics Committee Lokmanya Medical Research Centre. Additionally, the study was registered on the Clinical Trial Registry of India (CTRI) website with registration number CTRI/2024/12/078418 [Registered on: 23/12/2024]. The study was conducted as per approved protocol and Good Clinical Practices guidelines. The study was conducted, recorded, and reported strictly in accordance with Ayush/ ICH-GCP guidelines. Voluntary written informed consent from participants for their participation in the study was obtained. During the conduct of the clinical trial, rights, safety, and well-being of the study participants were given prime importance. The study drug was prepared with compliance to Good Manufacturing Practices (GMP) as applicable in India.

Participants

Inclusion Criteria

Male and female participants aged 30 to 65 years and BMI greater than 28 and less than 35 kg/m² were enrolled. Participants were required to be on OHAs, specifically a combination of biguanides and sulfonylureas. Newly diagnosed participants were permitted to begin the trial with investigational product monotherapy. Eligible participants had glycated hemoglobin (HbA1c) levels greater than 6.5% and less than 8% and fasting plasma glucose (FPG) levels greater than 130 mg/dL and less than 250 mg/dL. Participants with or without deranged lipid profiles were also included. Participants were required to be willing to comply with the study procedures and provide written informed consent.

Exclusion Criteria

Participants were excluded if they had been diagnosed with type 1 diabetes; individuals receiving antidiabetic drugs other than those permitted (including insulin). Participants with concurrent serious hepatic dysfunction (defined as AST and/or ALT greater than three times the upper normal limit), renal dysfunction (defined as serum creatinine >1.4 mg/dL), uncontrolled pulmonary dysfunction (including asthma and COPD), or any other severe concurrent illness were not eligible. Participants suffering from major systemic illnesses requiring long-term drug treatment, such as hematologic disorders, acute myocardial infarction, unstable angina, uncontrolled hypertension, congestive heart failure (class III or IV

NYHA), cerebrovascular accident, psychiatric or neurological disorders, autoimmune conditions, or those who had received chronic (>14 days) systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, intra-articular, or inhaled preparations) within six months prior to enrollment were also excluded. Smokers, alcoholics, individuals with a history of drug abusers, individuals with malignancy, those in other clinical trials, and pregnant or lactating women or those not using contraception were also excluded. Additionally, participants with any condition that could interfere with study completion or confound outcomes were not eligible.

Randomization and Allocation

This was a randomized clinical trial with four intervention arms. The present manuscript reports the comparative efficacy and safety outcomes of two selected treatment groups. Details are provided below:
Standard Berberine (Marketed active comparator): randomized n=22, completed n=22
Lipokon^{TM} Berberine: randomized n=22, completed n=22

Study Methodology

This randomized, double-blind, parallel-arm, prospective clinical trial evaluated the efficacy and safety of standardized extract of berberine supplementation in the management of T2DM. Participants in each group were advised to take two capsules thrice daily after meals. All participants received counselling on diet and lifestyle modifications at each visit. The treatment duration was 90 days.

Efficacy was assessed by evaluating fasting and post-meal plasma glucose levels, as well as anthropometric parameters (body weight, BMI, waist circumference), fasting insulin, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) scores. Lipid metabolism was evaluated by measuring cholesterol, LDL, HDL, and triglyceride levels. Additional assessments included Metabolic Syndrome Severity Z-score (MetS-Z), diabetes-related quality of life score (DQOL), and biochemical and hematological investigations such as LFT, RFT, and CBC at screening and at the end of the study. Safety assessments included monitoring of adverse events, vital signs, tolerability, and compliance throughout the study.

Blood samples were collected at screening and at the end of the study (day 90) to evaluate changes in glycemic profile, insulin resistance, lipid metabolism. For safety assessments, blood samples were collected at screening and day 90 to analyze hematological and biochemical parameters. All collected samples were processed and analyzed at a centralized NABL-accredited laboratory (My Labs Healthcare, Office No. 15, 1st Floor, Ganesham Commercial, Sai Nagar Park, Pimple Saudagar, Pune, Pimpri-Chinchwad, Maharashtra 411027).

Study Endpoints

The primary endpoints, changes in glycemic profile (fasting and post meal glucose levels) were assessed from screening to end of the study. While, HbA1c, fasting insulin, HOMA-IR score was assessed at screening and end of the study. Secondary endpoints of the study included assessment of changes in lipid metabolism (LDL, HDL, triglycerides, cholesterol), MetZ score and DQOL score was evaluated at screening and end of study. Anthropometric parameters (body weight, BMI and waist circumference) were assessed from screening to the end of the study.

Safety endpoints of the study were to evaluate LFT, RFT, CBC at screening and end of the study. Vitals, AEs, compliance and tolerability was assessed throughout the study.

Sample Size

The sample size was calculated for a four-arm parallel-group design. To ensure at least 80 evaluable participants, more than 80 individuals were planned to be enrolled, accounting for an anticipated 10% dropout rate. Participants were randomized equally in groups. For the current analysis, data from participants randomized to Standard Berberine (n = 22) and Lipokon™ Berberine (n = 22) were included.

Statistical Analysis

All analyses were done using SPSS software and a p value of less than 0.05 was considered statistically significant. All data were summarized with descriptive statistics (number of participants, mean, standard deviation, minimum, median, and maximum) for continuous endpoints and frequency and percentage for categorical endpoints. Primary and secondary efficacy endpoints were analyzed using the PP (per protocol) population and Safety variables as per mITT (modified intention-to-treat). The normality of the data distribution was assessed using the Kolmogorov–Smirnov test. Based on the distribution, within-group comparisons (from baseline to Day 90) were carried out using either the paired Student's t-test for normally distributed data or the Wilcoxon signed-rank test for non-parametric data. Categorical variables, including the incidence of adverse events and demographic features, were compared using the as frequency and percentages. Tolerability & compliance will be expressed as percentage.

OBSERVATION AND RESULTS

Of the 86 randomized participants, 22 in Standard Berberine and 22 in Lipokon™ Berberine were included in present analysis. The details are provided in CONSORT (Figure 1).

Assessment of Demographics

The study population included both male and female participants across both treatment groups. The number of male and female participants was comparable, and the mean age for each gender was similar, with no notable differences. Overall, the age distribution across all groups was well balanced, supporting the comparability of the treatment arms for further efficacy and safety assessments. Data represented in Table 1.

Assessment of Anthropometric Parameters

Anthropometric parameters include assessment of weight, BMI, and waist circumference. Both treatment groups showed significant reductions in body weight over 90 days, with Lipokon™ demonstrating the better efficacy. BMI decreased significantly from screening to day 90 in the Lipokon® (30.32±2.30 to 29.51±2.25) while minimal changes were seen with standard Berberine (29.58±1.65 to 29.33±1.89). Waist circumference remained largely unchanged across groups (Table 2).

Assessment of Glycemic Profile

Both treatment groups exhibited reductions in fasting plasma glucose with statistically significant improvements by Day 90. Lipokon™ Berberine showed a reduction (43.47%) comparable to Standard

Berberine (44.64%). Postprandial glucose levels also declined significantly by Day 90. Lipokon™ Berberine achieved a 43.57% reduction comparable to and numerically higher than that observed with Standard Berberine (38.11%). Both groups achieved statistically significant reductions in HbA1c by Day 90, with the greater improvement seen in Lipokon™ Berberine (23.49%) compared to Standard Berberine (23.16%). The observed reduction in HbA1c levels among diabetic participants, reflects a significant improvement in glycemic control. Data represented in Table 3.

Assessment of changes in Insulin resistance

By day 90, reduction of similar magnitude was observed for Standard Berberine (36.94%) and Lipokon™ (32.93%). Both formulations significantly reduced HOMA-IR values from screening, indicating improved insulin sensitivity. The Standard Berberine (65.75%) and Lipokon™ (64.45%) showed comparable reduction. Data represented in Table 4.

Assessment of Lipid Profile

The lipid profile assessment for most of the parameters showed significant improvements over 90 days. Total cholesterol and LDL levels were significantly reduced in both groups, with the greater reductions observed in Lipokon™ Berberine (28.18% and 38.24%) compared to Standard Berberine (21.63% and 29.83%). HDL cholesterol decreased slightly, triglycerides and VLDL cholesterol also showed significant within-group reductions (Table 5).

Assessment of Metabolic Syndrome Severity Z Score

Over the 90 days period, both treatment arms exhibited a statistically significant reduction in MetZ score. The percentage reduction across Lipokon™ Berberine (86.24%) and Standard Berberine group (88.31%) was comparable (Table 6).

Assessment of Diabetic Related Quality of Life Score

Both treatment groups showed significant improvements in Diabetic Related Quality of Life scores from screening to Day 90. Standard Berberine showed a 37.65% improvement, with scores decreasing from 41.41±5.47 at screening to 25.82±2.15 at day 90 and Lipokon™ Berberine demonstrated a 36.74% improvement, with scores reducing from 38.73±5.93 to 24.50±3.28. Data represented in Table 7.

Safety Assessment

Throughout the study period, both groups maintained stable vital sign parameters, including systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature, with values remaining within normal clinical limits. No clinically significant deviations or safety concerns were observed across any treatment, indicating good tolerability of the interventions.

Haematological parameters remained within normal physiological and clinical ranges both before and after the study duration, indicating a favourable safety profile. No clinically significant deviations were observed throughout the study.

A total of 10 events occurred in Lipokon™ Berberine (45.45%) and 8 in Standard Berberine (36.36%). Hyperacidity and constipation were the most commonly reported events. Fever and cold were rare.

Overall, both the total number of adverse events and the number of participants experiencing at least one event were similar across groups, indicating comparable tolerability of interventions.

Tolerability was assessed based on the incidence and severity of adverse events using a predefined scoring system (0 = poor, 1 = fair, 2 = good, 3 = excellent). The scores across both groups remained above 2, indicating a rating between good to excellent on the tolerability scale. Additionally, all participants demonstrated high compliance with the treatment regimen, with no individual missing more than three doses per month throughout the study

DISCUSSION

In this 90-day comparative study, both berberine formulations demonstrated significant improvements across multiple parameters associated with metabolic syndrome, including glycemic control, insulin sensitivity, lipid profiles, anthropometric measures, and overall quality of life. Lipokon™ Berberine demonstrated better performance compared to Standard Berberine in several key areas such as BMI, LDL and cholesterol. Improvements in fasting and postprandial glucose were observed across both groups, with greater reduction seen in Lipokon™ Berberine for PPG.

While both groups showed a favorable safety profile and tolerability, formulation-specific differences were evident in the magnitude of metabolic benefits. Lipokon® emerged as a strong overall performer in improving glycaemic parameters and reducing BMI. These findings support the enhanced clinical utility of novel berberine delivery systems over conventional formulations for comprehensive metabolic management.

Berberine demonstrates antidiabetic activity through multiple pathways relevant to our study findings. It enhances insulin sensitivity by upregulating insulin receptors, modulating insulin signaling pathways and reduces insulin resistance in target tissues [10]. Berberine activates adenosine monophosphate-activated protein kinase, promoting glycolysis and improving glucose utilization in adipose tissue and skeletal muscle [11]. Berberine demonstrates anti-inflammatory, antioxidant, antibacterial, and glucose-lowering properties making it a promising candidate for the therapeutic management of diabetes [12,13].

A study conducted to examine the effect of berberine on hepatic cholesterol biosynthesis in hyperhomocysteinemic rats showed improved liver function by inhibiting HMG-CoA reductase activity and reduced hepatic cholesterol content [14]. Another preclinical investigation proved that berberine is neuroprotective, antioxidative, and corrects diabetes-related neurochemical dysfunction [15].

A study evaluating the effectiveness and safety of berberine in treating type 2 diabetics with dyslipidaemia. showed berberine reduced fasting and post load plasma glucose, HbA1c, triglyceride, total cholesterol, and low-density lipoprotein-cholesterol [16]. Berberine is a potent oral hypoglycemic agent with beneficial effects on lipid metabolism [17].

In line with our findings, a pilot study demonstrated the efficacy and safety of berberine in managing type 2 diabetes mellitus, showing hypoglycemic effects comparable to metformin over a 3-month period. In newly diagnosed patients, berberine significantly reduced HbA1c, fasting, and postprandial glucose levels,

along with plasma triglycerides. Notably, no hepatic or renal toxicity was reported, though mild, transient gastrointestinal symptoms were observed in a subset of participants. These outcomes support berberine's potential as a safe and effective adjunctive treatment in type 2 diabetes mellitus [18].

Consistent with our observations, a recent meta-analysis of 50 randomized controlled trials involving 4,150 participants confirmed the efficacy and safety of berberine in the management of type 2 diabetes mellitus. BBR alone significantly improved glycemic parameters such as fasting plasma glucose, 2-hour postprandial glucose, and lipid profiles including LDL-C, total cholesterol, and triglycerides. When used in combination with standard hypoglycemic agents, Berberine further enhanced reductions in HbA1c, fasting insulin, HOMA-IR, and inflammatory markers, indicating synergistic metabolic benefits. The most commonly administered dosage ranged from 0.9 to 1.5 g/day over 1–3 months, with no serious safety concerns reported. These findings reinforce the potential role of Berberine as both a monotherapy and adjunctive treatment in T2DM management [19].

A clinical study evaluating the addition of berberine to metformin and acarbose in patients with newly diagnosed type 2 diabetes mellitus demonstrated superior efficacy compared to dual therapy alone. Patients receiving the triple combination therapy showed significantly greater reductions in fasting plasma glucose, 2-hour postprandial glucose, glycated hemoglobin, body mass index, and the homeostasis model assessment of insulin resistance. Importantly, the incidence of adverse effects was comparable between groups, indicating that the formulation did not compromise safety while enhancing glycemic and inflammatory outcomes [20]. The findings align with our study, where berberine similarly led to improved glycemic control and maintained a favorable safety profile.

The study on the Ayurvedic polyherbal formulation (PHF) containing an herbal combination of *B. aristata* and *E. officinalis,* shows significant reductions in fasting and postprandial glucose, along with a comparable reduction in HbA1c to metformin over 24 weeks. Additionally, PHF showed lipid-lowering effects, particularly in reducing total cholesterol levels. The study also confirmed that PHF maintained stable liver and renal function, ensuring its safety for long-term use. These findings support PHF as an adjunct for type 2 diabetes, enhancing glycemic control and metabolic health [21]. Similar results were observed in our study.

This preclinical study investigated the protective role of berberine on pancreatic β-cell function and oxidative stress in a diabetic rat model induced by streptozotocin and a high-fat, high-carbohydrate diet. Treatment with berberine at doses of 150 and 300 mg/kg for 16 weeks resulted in improved insulin secretion, enhanced insulin sensitivity, and increased antioxidant enzyme activity, along with a reduction in malondialdehyde levels. Histopathological examination revealed preservation of β-cell integrity with less mitochondrial and endoplasmic reticulum damage. These outcomes highlight berberine's ability to promote β-cell regeneration, enhance antioxidant defense, and reduce lipid peroxidation [22]. Consistent with our findings, this study further supports the antidiabetic potential of Berberis aristata, emphasizing its therapeutic relevance in managing prediabetes by improving glycemic parameters, insulin sensitivity, and lipid homeostasis.

A previous randomized, placebo-controlled clinical study investigated the efficacy of Berberis fruit extract (HIMABERB®) in prediabetic individuals over 12 weeks. The intervention led to significant reductions in fasting plasma glucose, 2-hour oral glucose tolerance, HbA1c, fasting insulin, and HOMA-IR, with FPG and 2h-OGTT values falling below prediabetes thresholds. These findings are consistent with our study on *Berberis aristata* improved glycemic control [23]. The comparable outcomes highlight the shared mechanism, such as improved insulin sensitivity and supporting the therapeutic potential of plant-based strategies in managing early-stage metabolic disturbances.

In summary, our study demonstrated that *Berberis aristata* supplementation significantly improved glycemic parameters, insulin sensitivity, lipid profile, & quality of life in individuals with type 2 DM. The strengths of this trial include its randomized, controlled design, use of a well-characterized single botanical extract, and multidimensional assessment of health. These outcomes are consistent with prior evidence supporting the antidiabetic potential of *Berberis* species. However, limitations such as the short intervention duration, absence of long-term follow-up, and limited sample size should be considered when interpreting the results. Further large-scale, long-term studies are warranted to validate and expand on these findings.

Conclusion

Over the 90-day clinical study, both berberine-based formulations, Standard Berberine (marketed comparator) and Lipokon™ Berberine demonstrated significant improvements across a range of metabolic, glycemic, and lipid parameters. Lipokon™ Berberine formulation resulted in greater weight reduction compared to Standard Berberine. HbA1c reduction was highest in Lipokon™ Berberine followed by standard berberine. Both interventions demonstrated excellent safety and tolerability. No serious adverse events occurred, and no participants discontinued due to adverse effects. Vitals, hematological, and biochemical parameters remained within normal clinical ranges throughout the study. This 90-day study demonstrated that both berberine-based formulations significantly improved metabolic, glycemic, and lipid parameters in adults. Lipokon™ Berberine showed comparable or superior trends to the standard comparator, with excellent safety and tolerability across groups.

Conflict of Interest: Dr. Praful Patil, Dr. Saraswati Gupta, Mr. Hiral Panchal, Mr. Ajay Pathak, and Mr. Vedant Gupta are employees of Konark Herbal and Healthcare Pvt. Ltd., the sponsor of the study. Mr. Vedant Gupta is a Director of Konark Herbal and Healthcare Pvt. Ltd. Dr. Ramshyam Agarwal, the Principal Investigator, declares no competing financial or non-financial interests related to this study.

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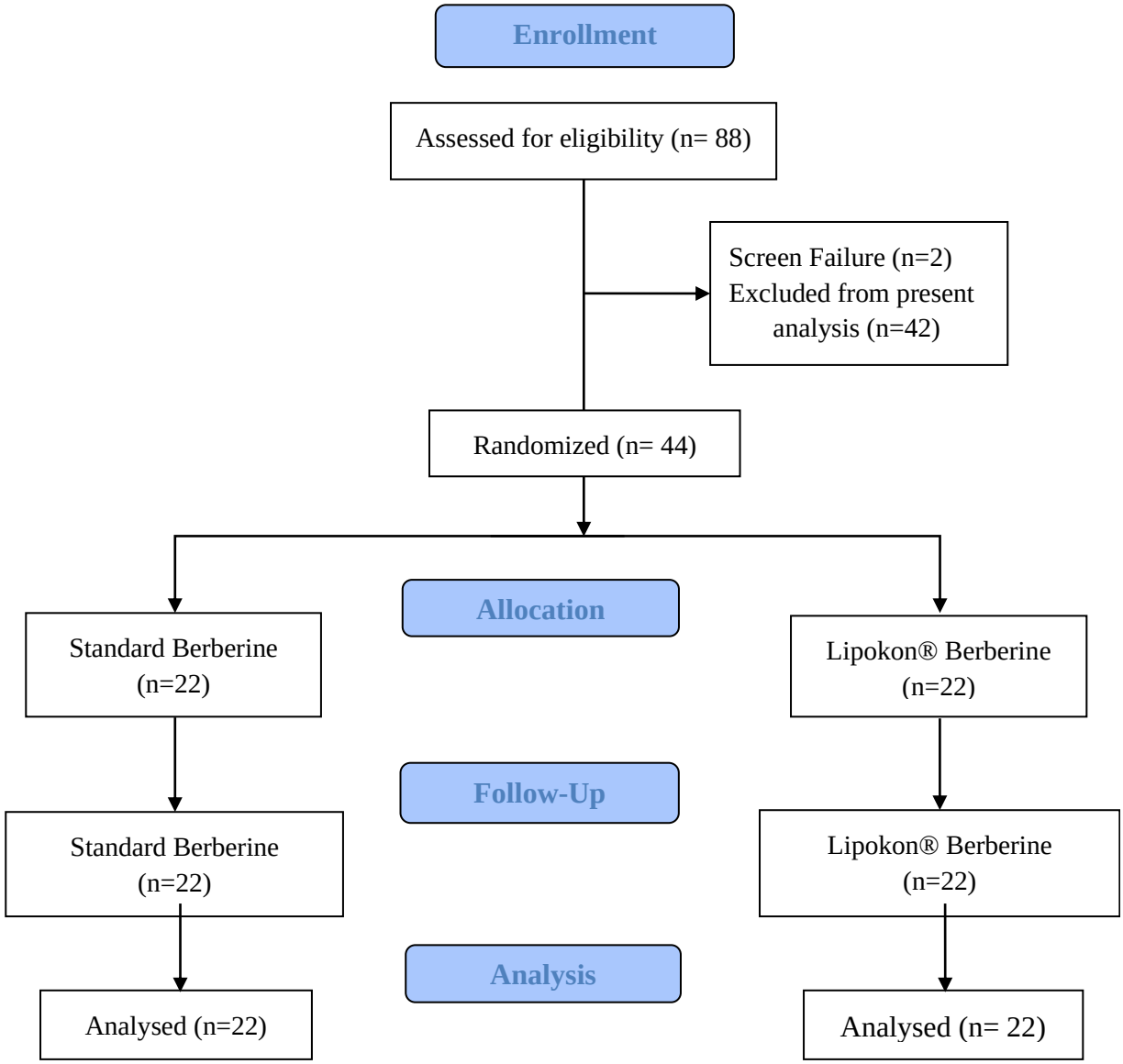
Abbreviations:

Abbreviation	Full Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
CRO	Clinical Research Organization
OHA	Oral Hypoglycemic Agents
AE	Adverse Event
SAE	Serious Adverse Event
BMI	Body Mass Index
DQOL	Diabetes-Related Quality Of Life Score
IP	Investigational Product
MetZ Score	Metabolic Syndrome Severity Z Score
HDL	High-Density Lipoprotein
SBP	Systolic Blood Pressure
LDL	Low-Density Lipoprotein
SPSS	Statistical Package For The Social Sciences
PP	Per Protocol
mITT	Modified Intention To Treat
FPG	Fasting Plasma Glucose
HbA1c	Hemoglobin A1c
T2DM	Type 2 Diabetes Mellitus
CVD	Cardiovascular Disease
AMPK	AMP-activated Protein Kinase
HDL	High-Density Lipoprotein
LDL	Low-Density Lipoprotein
HOMA IR	Homeostasis Model Assessment of Insulin Resistance
LFT	Liver Function Test
RFT	Renal Function Test
EC	Ethics Committee
CTRI	Clinical Trial Registry of India
HMG-CoA	Hydroxy-3-Methylglutaryl Coenzyme A
BER	Berberine
AChE	Acetylcholinesterase
AST	Aspartate Aminotransferase
ALT	Alanine Aminotransferase
COPD	Chronic Obstructive Pulmonary Diseases
IP	Investigational Product
SE	Serious Event
ICF	Informed Consent Form

Abbreviation	Full Form
CI	Confidence Interval
QA	Quality Assurance
QC	Quality Control
CONSORT	Consolidated Standards Of Reporting Trials

Figures

Figure 1: CONSORT diagram for the study.



Tables

Table 1: Assessment of demographics

Demographic details				
Group	**Male**	**Age (years)**	**Female**	**Age (years)**
Lipokon™ Berberine	13	47.08± 12.30	09	51.11± 12.41
Standard Berberine (Marketed active comparator)	14	45.50± 9.18	08	52.00± 10.01

Data is represented as Mean ± S.D.

Table 2: Assessment of Anthropometric parameters

Visits / Groups	Screening	Day 30	P-value within	Day 60	P-value within	Day 90	P-value within
Weight (Kg)							
Lipokon™ Berberine	70.67±11.80	70.06±11.76 (0.61Kg)	< 0.001	69.44±11.74 (1.23Kg)	< 0.001	68.81±11.70 (1.86Kg)	< 0.001
Standard Berberine (Marketed active comparator)	76.25±7.30	75.66±7.3 (0.59Kg)	< 0.001	75.66±7.3 (0.59Kg)	< 0.001	74.61±7.11 (1.64Kg)	< 0.001
BMI (Kg/m^2)							
Lipokon™ Berberine	30.32±2.30	30.05±2.27 (0.87%)	< 0.001	29.79±2.24 (1.75%)	< 0.001	29.51±2.25 (2.67%)	< 0.001
Standard Berberine (Marketed active comparator)	29.58±1.65	29.73±1.97 (0.52%)	0.551	29.73±1.97 (0.52%)	0.551	29.33±1.89 (0.85%)	0.326

Data is represented as Mean ± S.D (percent change). Within-group analysis was analysed by Student's t dependent test. P-value is significant at $p<0.05$.

Table 3: Assessment of Glycemic profile

Glycaemic profile							
Visits / Groups	**Screening**	**Day 30**	**P-value within**	**Day 60**	**P-value within**	**Day 90**	**P-value within**
Fasting plasma glucose (mg/dL)							
Lipokon™ Berberine	178.28±33.73	157.82±16.09 (11.48%)	0.039	149.05±13.55 (16.40%)	<0.001	100.77±12.49 (43.47%)	<0.001

Standard Berberine (Marketed active comparator)	179.00±32.28	145.68±18.93 (18.61%)	<0.001	158.27±10.48 (11.58%)	0.007	99.09±11.33 (44.64%)	<0.001
Post-meal plasma glucose (mg/dL)							
Lipokon™ Berberine	232.93± 85.83	170.86± 20.59 (26.65%)	0.003	166.59± 14.27 (28.48%)	0.001	131.45± 10.93 (43.57%)	<0.001
Standard Berberine (Marketed active comparator)	209.24± 88.44	176.09± 18.92 (15.84%)	0.086	159.64± 13.64 (23.71%)	0.018	129.50± 12.70 (38.11%)	<0.001
HbA1C (%)							
Lipokon™ Berberine	7.39±0.48	-	-	-	-	5.65± 0.61 (23.49%)	<0.001
Standard Berberine (Marketed active comparator)	7.28±0.54	-	-	-	-	5.60±0.51 (23.16%)	<0.001

Data is represented as Mean ± S.D (percent change). Within-group analysis was analysed by Student's t dependent test. P-value is significant at $p<0.05$.

Table 4: Assessment of changes in Fasting insulin & HOMA-IR

Visits / Group	Screening	Day 90	P-value (Within)
Fasting Insulin (mIU/L)			
Lipokon™ Berberine	21.70±15.78	14.55±5.11 (32.93%)	0.053
Standard Berberine (Marketed active comparator)	27.97±29.19	17.64±6.39 (36.94%)	0.211
HOMA-IR			
Lipokon™ Berberine	10.13±9.42	3.60±1.34 (64.45%)	0.004
Standard Berberine (Marketed active comparator)	12.74±13.86	4.36±1.76 (65.75%)	<0.001

Data is represented as Mean ± S.D (percent change). Within-group analysis was analysed by Student's t-dependent test and Wilcoxon Signed-Rank Test. P-value is significant at $p<0.05$.

Table 5: Assessment of lipid profile

Total Cholesterol (mg/dL)			
Visits / Group	**Screening**	**Day 90**	**P-value (Within)**
Lipokon™ Berberine	203.72±47.62	146.31±16.47 (28.18%)	< 0.001
Standard Berberine (Marketed active comparator)	192.34±34.31	150.75±9.55 (21.63%)	< 0.001
LDL Cholesterol (mg/dL)			
Lipokon™ Berberine	117.24±34.61	72.41±11.46 (38.24%)	< 0.001
Standard Berberine (Marketed active comparator)	108.76±29.30	76.32±10.38 (29.83%)	< 0.001
Cholesterol HDL Direct (mg/dL)			
Lipokon™ Berberine	54.56±12.30	49.55±6.36 (9.18%)	0.122
Standard Berberine (Marketed active comparator)	50.61±9.12	49.77±6.11 (1.65%)	0.746
Triglycerides (mg/dL)			
Lipokon™ Berberine	159.61±68.60	121.77±25.11 (23.71%)	0.009
Standard Berberine (Marketed active comparator)	164.84±64.06	123.27±20.11 (25.22%)	0.006
VLDL Cholesterol (mg/dL)			
Lipokon™ Berberine	31.92±13.72	24.35±5.02 (23.71%)	0.009
Standard Berberine (Marketed active comparator)	32.97±12.81	24.65±4.02 (25.22%)	0.006
Cholesterol/HDL ratio			
Lipokon™ Berberine	3.78±0.74	2.97±0.24 (21.53%)	< 0.001
Standard Berberine (Marketed active comparator)	3.87±0.79	3.07±0.38 (20.70%)	< 0.001
LDL/HDL Ratio			
Lipokon™ Berberine	2.20±0.67	1.47±0.24 (33.09%)	< 0.001
Standard Berberine (Marketed active comparator)	2.21±0.69	1.56±0.34 (29.07%)	0.001

Data is represented as Mean ± S.D (percent change). Within-group analysis was analysed by Student's t dependent test. P-value is significant at p<0.05.

Table 6: Assessment of Metz Score

Visits / Groups	Screening	Day 90	P-value within
Lipokon™ Berberine	1.36±0.77	0.19±0.30 (86.24%)	< 0.001
Standard Berberine (Marketed active comparator)	1.50±0.70	0.17±0.29 (88.31%)	< 0.001

Data is represented as Mean ± S.D (percent change). Within-group analysis was analysed by Student's t-dependent test and Wilcoxon Signed-Rank Test. P-value is significant at p<0.05.

Table 7: Assessment of Daily Quality of Life score

Daily Quality of Life score			
Visits / Groups	**Screening**	**Day 90**	**P-value within**
Lipokon™ Berberine	38.73±5.93	24.50±3.28 (36.74%)	< 0.001
Standard Berberine (Marketed active comparator)	41.41±5.47	25.82±2.15 (37.65%)	< 0.001

Data is represented as Mean ± S.D (percent change). Within-group analysis was analysed by Student's t dependent test. P-value is significant at p<0.05.