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Original Research Article

Metaberine (bio-optimised berberine 200 mg/day) improves metabolic health markers in healthy adults: a randomized, double-blind and placebo-controlled crossover trial

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ABSTRACT

Background: Berberine shows promise for metabolic health but suffers from poor bioavailability requiring high daily doses (500–1500 mg/day) that frequently cause gastrointestinal side effects. We evaluated whether a biooptimised berberine formulation (Metaberine™) developed using BioSOLVE technology could provide meaningful metabolic benefits at substantially lower doses.

Methods: In this randomized, double-blind, placebo-controlled crossover trial, 36 healthy adults (mean age 39.9 years, BMI 25.8 kg/m²) with fasting glucose 100–125 mg/dl received Metaberine™ 200 mg or placebo once daily for 14 days per period (7-day washout). Primary outcomes were fasting and postprandial blood glucose during a 75 g oral glucose tolerance test (OGTT) at 0, 30, 60, 90 and 120 minutes. Secondary outcomes included plasma GLP-1, glucose concentration parameters (AUClast, Cmax), lipid profile and safety.

Results: Metaberine™ significantly improved all glycemic parameters: fasting glucose decreased by 9.08 mg/dl versus 1.36 mg/dl with placebo ($p<0.0001$), with significant reductions at all postprandial timepoints. Baseline-corrected glucose AUClast and Cmax decreased by 13.5% and 12.7%, respectively (both $p<0.0001$). Plasma GLP-1 increased by 29% (fasting) and 22% (postprandial) with Metaberine™ versus minimal change with placebo (both $p<0.0001$). Lipid profiles improved with decreases in total cholesterol and LDL-C and an increase in HDL-C. Safety was excellent with 100% participant retention and no supplement-related adverse events.

Conclusions: These findings demonstrate that biooptimised berberine at 200 mg/day a 5–7-fold lower dose than conventional formulations significantly improve glycemic control, enhances incretin response and favorably modulates lipid metabolism in healthy adults at metabolic risk, supporting its potential as a functional nutritional ingredient for metabolic wellness.

Keywords: Berberine, Biooptimised, GLP-1, Glycemic control, Metabolic health, Metaberine

INTRODUCTION

Maintenance of optimal metabolic health represents a cornerstone of long-term wellbeing, particularly in the context of rising global rates of overweight, obesity and metabolic dysfunction. Globally, excess body weight and obesity affect more than 1 billion adults and are closely associated with dysregulated glucose homeostasis,

impaired lipid metabolism and increased cardiometabolic risk, even in individuals without overt diabetes.[1] Postprandial metabolic disturbances, characterized by exaggerated glucose excursions and impaired metabolic flexibility, contribute to insulin resistance, low-grade inflammation and progressive weight gain, thereby accelerating the transition toward metabolic disease.[2]

Among the physiological regulators of postprandial metabolism, glucagon-like peptide-1 (GLP-1) plays a central role in maintaining glycemic stability and energy balance. GLP-1 enhances glucose-dependent insulin secretion, suppresses glucagon release, delays gastric emptying and modulates appetite and lipid metabolism.[3,4] Attenuated endogenous GLP-1 secretion and responsiveness are observed in individuals with overweight, obesity and insulin resistance, contributing to impaired postprandial glycemic control and dysregulated energy intake.[4,5] Consequently, strategies that enhance endogenous GLP-1 responses represent biologically aligned approaches for supporting metabolic resilience and cardiometabolic health in at-risk populations.[5]

Lifestyle modification remains the foundation of metabolic health maintenance; however, sustained adherence to dietary and physical activity interventions remains challenging in real-world settings, particularly over extended durations.[6] As a result, there is growing interest in safe, well-tolerated nutritional alternatives that can complement lifestyle measures by targeting key metabolic pathways, including postprandial glycemia, incretin biology and lipid metabolism, while avoiding the limitations often associated with pharmacological treatments.

Berberine, a naturally occurring isoquinoline alkaloid derived from botanical sources such as *Coptis chinensis* and *Phellodendron amurense*, demonstrates beneficial effects on glucose and lipid metabolism in multiple clinical and preclinical studies.[7,8] Mechanistic investigations indicate that berberine activates AMP-activated protein kinase (AMPK), enhances insulin receptor expression, modulates gut microbiota composition and influences incretin secretion and related signaling pathways.[9,10] Several meta-analyses and systematic reviews have reported significant improvements in fasting and postprandial glucose levels, lipid parameters and markers of insulin sensitivity following berberine supplementation.[11,12] These metabolic effects position berberine as a promising nutritional supplement for supporting overall metabolic health.

Despite its demonstrated efficacy, conventional berberine is characterized by extremely poor oral bioavailability (approximately 2%), resulting from low aqueous solubility, limited intestinal permeability, active efflux by transport proteins and extensive first-pass metabolism.[13] Consequently, high daily doses (typically 500–1500 mg administered in divided doses) are required to achieve meaningful systemic exposure, often leading to gastrointestinal discomfort such as nausea, diarrhoea and constipation in a substantial proportion of users, thereby limiting compliance and long-term use.[14,15]

Recent advances in formulation science have focused on overcoming these bioavailability challenges through approaches such as phytosome complexation, nanoparticle delivery systems and other enrichment technologies.[16] BioSOLVE technology is designed to encapsulate water-insoluble active compounds within a food-grade, water-soluble polysaccharide matrix, enabling delivery of actives at the submicron scale and enhancing water solubility, stability and functional performance. BioSOLVE technology has been employed in the formulation of Metaberine™ to enhance the solubility and intestinal permeability of berberine without chemical modification. Pharmacokinetic evaluations demonstrate substantially increased systemic exposure, including approximately nine-fold higher area under the concentration–time curve (AUC) and enhanced maximum plasma concentration compared with conventional berberine formulations at equivalent doses.[17] This enables effective supplementation at a low daily dose of 200 mg, with the potential to minimize dose-related gastrointestinal intolerance while preserving metabolic benefits.[18]

While clinically reported studies have evaluated high-dose standard berberine formulations in individuals with established metabolic disease, limited clinical evidence exists on the metabolic effects of low-dose, biooptimised berberine in non-diabetic adults at metabolic risk.[19] In particular, data examining the impact of biooptimised berberine on postprandial glycemia, endogenous GLP-1 response and lipid metabolism in healthy populations remain scarce. For this reason, we conducted a randomized, double-blind, placebo-controlled crossover clinical study to examine the effects of Metaberine™ supplementation on postprandial glycemic regulation as the primary outcome, while also assessing incretin response, glucose exposure parameters, lipid metabolism and safety as secondary outcomes.

METHODS

Study design

The study was designed as a randomized, double-blind, placebo-controlled, crossover clinical trial. Healthy adults aged 19–70 years (both inclusive) were included in the study as per the inclusion and exclusion criteria. The study was carried out at the BGS Global Institute of Medical Sciences, Bengaluru, Karnataka, India after obtaining written informed consent from all participants. The study was initiated after approval (Reference number: BGS GIMS IEC/APP/JUL/10/2025-2026) from the Institutional Ethics Committee of the BGS Global Institute of Medical Sciences, Bengaluru, Karnataka, India and registered with the Clinical Trials Registry –

India on 26 Aug 2025, with the registration number CTRI/2025/08/093675. The study was conducted in accordance with ICH-GCP guidelines, ethical principles that have their origin in the Declaration of Helsinki and with local regulations.

The study included five visits in total, consisted of two 14 days treatment periods separated by a 7 days washout period. At visit 1 (screening, day −7 to 0), eligible participants gave informed consent, went through screening procedures and received instructions on diet, physical activity and how to keep their study diary. They were asked to continue their usual diet and routine physical activity and to avoid any unusually intense or new exercise during the duration of entire study. Those who met the eligibility criteria were then randomly assigned 1:1 to take either one capsule of the test product or placebo once daily for the first 14-day period (period 1). Visit 2 (period 1, day 1) was the baseline visit for the first treatment period and visit 3 (period 1, day 14±1) was the end of period assessment for that phase. After a 7 day washout, participants switched to the other supplement (placebo or test product) for the second 14 day period (period 2). Visit 4 (period 2, day 1) served as the baseline for the second treatment and visit 5 (period 2, day 14±1) was the final, end of study visit.

Participants

Participants were screened and selected based on predefined inclusion and exclusion criteria. Eligible participants were healthy male and female adults aged 19–70 years (both inclusive) with a body mass index (BMI) ≤30 kg/m². Specifically, participants were required to have a fasting blood glucose between 100 mg/dl and 125 mg/dl and a 2-hour postprandial blood glucose between 140 mg/dl and 199 mg/dl on a standardized 75g oral glucose tolerance test (OGTT) at screening, consistent with the American Diabetes Association diagnostic criteria for impaired fasting glucose and impaired glucose tolerance respectively (American Diabetes Association, 2025). These thresholds were chosen to enrich enrolment with healthy adults demonstrating measurable glycemic responses, the target population for the intervention.

Female participants of childbearing potential were required to have a negative urine pregnancy test at screening and to agree to use approved contraception throughout the study period. All participants were required to maintain their habitual diet and lifestyle and to provide written informed consent prior to performing study procedures. Participants were excluded if they had fasting plasma glucose ≥126 mg/dl, random plasma glucose ≥200 mg/dl or glycated hemoglobin (HbA1c) ≥6.5% or a known diagnosis of type 1 or type 2 diabetes mellitus. Individuals currently using medications or dietary supplements known to influence glucose metabolism were also excluded. Additional exclusion criteria included clinically significant chronic medical conditions such as cardiovascular, hepatic, renal, respiratory, endocrine or other systemic diseases; uncontrolled hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg); uncontrolled thyroid disorders; pregnancy or lactation; participation in another clinical trial within 30 days prior to enrolment; known hypersensitivity to any component of the investigational supplement; history of substance abuse or excessive alcohol consumption; or any condition that, in the investigator's opinion, could interfere with study participation, assessment of outcomes, compliance with the protocol or completion of the study.

Interventions, randomization and blinding

Metaberine™ a bio-optimized berberine, the test substance evaluated in this study, manufactured using proprietary BioSOLVE technology, was filled into opaque colored capsules. Each capsule contained 200 mg of bio-optimized berberine (Metaberine™). Similar-looking placebo capsules were prepared using microcrystalline cellulose. Both the test product and placebo capsules were manufactured by Zeus Hygia Life Sciences Pvt Ltd, Hyderabad, India.

All randomized participants were instructed to take the assigned capsule once daily, 30 minutes before a meal, for 14 days in each period and were instructed to record the date and time of intake in their subject diary.

Randomization was performed using a block randomization schedule generated by R statistical software. Each randomized participant received a unique randomization number. Participants were randomly assigned to two supplement sequences in a 1:1 ratio. The study was conducted as a double-blind trial; both the investigators and the participants were unaware of the intervention allocation.

Concomitant medication use was recorded throughout the study. Eight participants received non prohibited medications for short term intercurrent conditions, such as oral rehydration salts, paracetamol and a pantoprazole/domperidone combination in one case; the investigator confirmed that none of these were likely to have a meaningful impact on the efficacy outcomes.

Outcomes

The primary objectives were to evaluate the effects of Metaberine™ on fasting blood glucose and postprandial blood glucose via 75g OGTT compared to placebo. Mean changes in fasting and postprandial glucose measured at 0, 30-, 60-, 90- and 120-minutes post-glucose challenge from baseline to end of supplementation. The secondary objectives were to assess the impact of Metaberine™ on GLP-1 levels, glucose concentration parameters (AUClast, AUCinf and Cmax), lipid profile (total cholesterol, LDL-C, HDL-C, VLDL) and safety profile.

Fasting and postprandial blood glucose

Following a 75g glucose load, venous blood samples were collected at 0 (fasting), 30, 60, 90 and 120 minutes. Glucose was measured using the glucose oxidase method on an automated analyzer. Changes from period-specific baseline to end of each 14-day supplementation period were calculated for each timepoint.

Oral glucose tolerance test dosing procedure

At the baseline assessment visit (day 1 of each period), the OGTT was performed in the fasting state without prior product administration. At the day 14 follow-up visit, participants consumed their assigned capsule at the study site and, 60 minutes later, underwent the standardized 75 g oral glucose challenge, consistent with the intended real-world pre-meal dosing regimen. This procedure was applied identically during both the Metaberine™ and Placebo supplementation periods.

Glucagon-like peptide-1

Plasma GLP-1 concentrations were measured using a validated enzyme-linked immunosorbent assay (ELISA) in EDTA-treated plasma samples collected at fasting (0 min) and at 120 minutes following the oral glucose load. Blood samples were immediately centrifuged at 3000 rpm for 4 minutes using a refrigerated laboratory centrifuge to separate plasma. The plasma samples were aliquoted and stored at −80°C until analysis.

Glucose concentration parameters

Glucose concentration parameters were calculated using the trapezoidal rule from OGTT data. AUClast represents the area under the curve from 0 to 120 minutes. Both non-baseline-corrected and baseline-corrected values were calculated. C_{max} (peak glucose concentration) was the maximum concentration observed during OGTT. AUC inf (AUC extrapolated to infinity) was calculated in participants whose OGTT concentration–time profile provided sufficient post-peak data points for reliable terminal phase extrapolation, AUCinf analyses are therefore based on a subset of participants and should be considered exploratory.

Lipid profile

Fasting measurements of total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and very-low-density lipoprotein (VLDL) were performed using enzymatic methods on an automated chemistry analyzer.

Anthropometric measures

Body weight and BMI of each participant were recorded at each visit. Changes in body weight (kg) and BMI (kg/m^2) from baseline to end of each 14-day supplementation period were assessed as secondary outcomes.

Safety assessments

Safety parameters were assessed at baseline and at the end of each supplementation period through physical examination, documentation of vital signs (blood pressure, heart rate, respiratory rate and temperature) and evaluation of clinically significant changes in laboratory parameters including complete blood count (CBC), serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), blood urea nitrogen (BUN) and serum creatinine. All adverse events (AEs) and serious adverse events (SAEs) were monitored and documented, with particular attention to gastrointestinal symptoms.

Statistical methods

The sample size was calculated using the standard formula for comparison of two means in a crossover design. Assuming a clinically meaningful difference of 15 mg/dl in postprandial glucose between interventions, a standard deviation of 20 mg/dl, 80% statistical power and a two-sided alpha of 0.05, a minimum of 30 evaluable participants was required. Considering the 15% dropout rate, 36 participants were enrolled in this study.

Data were analyzed using SAS/SPSS statistical software. We present descriptive statistics (mean±standard deviation) for baseline and day 14 values to characterize the observed data within each treatment period.

For primary statistical inference, we have used a linear mixed model (LMM) for crossover trial design in the present study. This model included treatment (Metaberine™ vs. Placebo), period (period 1 vs. period 2), sequence (AB vs. BA) and carryover effect as fixed effects, with subject included as a random effect to account for within-subject correlation. Treatment effects are reported as estimated marginal means (also called least-squares means), which represent model-based predictions adjusted for period, sequence and other design factors. Authors report treatment differences with their standard errors (SE), 95% confidence intervals (CI) and p values. Statistical significance was assessed at the conventional two-sided α=0.05 threshold. This analytical approach aligns with current regulatory guidance for crossover studies and properly controls for potential confounding due to period and sequence effects.

As all 36 randomized participants completed the study per protocol without major deviations, the per-protocol, intention-to-treat and safety analysis populations were identical (n=36). All continuous study assessments were summarized by intervention and timepoint using descriptive statistics (n, mean, standard deviation). All categorical assessments were summarized using frequency counts and percentages. Hypothesis testing was two-sided and performed at the 0.05 significance level.

RESULTS

Participants' flow

The study was initiated in July 2025 and completed in October 2025. 48 participants were assessed for eligibility; 12 did not meet inclusion criteria (7 due to fasting glucose ≥126 mg/dl, 3 due to HbA1c ≥6.5%, 2 declined participation) and were excluded at screening. The remaining 36 eligible participants were randomized 1:1 to one of two treatment sequences: Sequence A (n=18; Metaberine™ in Period 1, then Placebo in Period 2) and Sequence B (n=18; Placebo in Period 1, then Metaberine™ in Period 2). All 36 participants (19 males, 17 females) completed Period 1, the 7-day washout and Period 2, achieving 100% retention. Compliance with the assigned supplement exceeded 98% in both periods. As all participants received both treatments in the crossover design, data from all 36 participants contributed to each treatment comparison. No statistically significant carryover effects were identified.

Baseline demographic characteristics

The study included 19 (52.8%) males and 17 (47.2%) females of Indian origin. Baseline demographic characteristics are presented in Table 1. Demographic parameters were comparable between the two randomization sequences with no significant differences (p>0.05).

Effect of Metaberine™ on glycemic control

Fasting and postprandial blood glucose

The primary efficacy outcomes are presented in Table 2. Participants receiving Metaberine™ showed a reduction in fasting glucose from 116.19±5.24 mg/dl at baseline to 107.11±5.64 mg/dl at Day 14, representing a mean within-period decrease of 9.08±3.52 mg/dl. In contrast, the placebo group exhibited a smaller change from 114.08±5.48 mg/dl to 112.72±6.31 mg/dl (mean change −1.36±2.71 mg/dl). When analyzed using the linear mixed model to adjust for period, sequence and carryover effects, the adjusted treatment difference was −1.75 mg/dl (SE=0.63, 95% CI: −3.0 to −0.5 mg/dl, p=0.0068), with estimated marginal means of 112 mg/dl for Metaberine™ versus 113 mg/dl for placebo. A significant period effect was observed (p<0.0001), though no significant sequence (p=0.42) or carryover (p=0.86) effects were detected, confirming the validity of the crossover design.

Metaberine™ showed clinically significant improvements in postprandial glucose excursions at all OGTT timepoints compared to placebo (Figure 1). At 30 minutes post-glucose challenge, Metaberine™ reduced glucose levels from 182.00±11.51 mg/dl to 167.33±12.66 mg/dl (mean change −14.67±6.08 mg/dl), while placebo showed minimal change from 179.81±10.86 mg/dl to 178.69±11.13 mg/dl (mean change −1.11±2.63 mg/dl). Linear mixed model analysis yielded an adjusted supplement effect of −4.58 mg/dl (SE=0.97, 95% CI: −6.5 to −2.7 mg/dl, p<0.0001), with estimated marginal means of 175 mg/dl for Metaberine™ versus 179 mg/dl for placebo. A significant period effect was noted (p<0.0001), with no significant sequence or carryover effects (p=0.79 and p=0.13, respectively).

The clinically significant effect occurred at 60 minutes, where Metaberine™ decreased glucose from 193.28±6.35 mg/dl to 171.64±7.77 mg/dl (mean change −21.64±5.76 mg/dl, representing an 11% reduction). Conversely, the placebo group showed a slight increase from 190.94±8.16 mg/dl to 194.08±7.85 mg/dl (mean change +3.14±4.56 mg/dl). The linear mixed model analysis revealed an adjusted supplement effect of −10.10 mg/dl (SE=1.41, 95% CI: −12.9 to −7.3 mg/dl, p<0.0001), with estimated marginal means of 182 mg/dl for Metaberine™ compared to 193 mg/dl for placebo. Period effect remained significant (p<0.0001), while sequence and carryover effects were not detected (p=0.91 and p=0.83, respectively).

This improvement pattern continued at 90 minutes, where the Metaberine™ group showed a reduction from 175.03±6.11 mg/dl to 156.94±6.90 mg/dl (mean change −18.08±5.34 mg/dl), while the placebo group exhibited an increase from 173.03±8.21 mg/dl to 177.08±6.81 mg/dl (mean change +4.06±6.36 mg/dl). Linear mixed model analysis demonstrated an adjusted supplement effect of −9.07 mg/dl (SE=1.31, 95% CI: −11.6 to −6.5 mg/dl, p<0.0001), with estimated marginal means of 166 mg/dl for Metaberine™ versus 175 mg/dl for placebo. A significant period effect was present (p=0.0006), while sequence and carryover effects were not significant (p=0.98 and p=0.76, respectively).

At 120 minutes, the Metaberine™ group maintained the downward trend with values declining from 162.17±6.57 mg/dl to 146.78±7.89 mg/dl (mean change −15.39±3.76 mg/dl), whereas the placebo group showed an increase from 160.08±7.62 mg/dl to 164.14±5.95 mg/dl (mean change +4.06±5.80 mg/d). Linear mixed model analysis yielded an adjusted supplement effect of −7.64 mg/dl (SE=1.16, 95% CI: −9.9 to −5.4 mg/dl, p<0.0001), with estimated marginal means of 154 mg/dl for Metaberine™ versus 162 mg/dl for placebo. Period effect was significant (p=0.0002), while sequence and carryover effects showed no significance (p=0.70 and p=0.55, respectively).

Effect on incretin response

Glucagon-like peptide-1

GLP-1 levels increased significantly with Metaberine™ supplementation at both measurement timepoints (Table 3). Fasting GLP-1 increased from 8.24±1.48 pg/ml to 10.64±2.03 pg/ml in the Metaberine™ group (mean change +2.40±1.78 pg/ml), while placebo showed minimal change from 8.35±1.52 pg/ml to 8.56±1.48 pg/ml (mean change +0.21±0.37 pg/ml). Linear mixed

model analysis demonstrated an adjusted treatment difference of +0.99 pg/ml (SE=0.20, 95% CI: +0.6 to +1.4 pg/ml, p<0.0001), with estimated marginal means of 9.45 pg/ml for Metaberine™ compared to 8.46 pg/ml for placebo. Period effect was significant (p<0.0001), while sequence and carryover effects were not (p=0.56 and p=0.92, respectively).

Postprandial GLP-1 at 120 minutes demonstrated substantial improvement with Metaberine™, increasing from 18.83±2.71 pg/ml to 22.93±2.80 pg/ml (mean change +4.09±1.71 pg/ml). In contrast, placebo supplementation was associated with a slight decrease from 18.62±1.64 pg/ml to 18.24±1.53 pg/ml (mean change −0.38±0.47 pg/ml). Linear mixed model analysis revealed an adjusted supplement effect of +2.45 pg/ml (SE=0.33, 95% CI: +1.8 to +3.1 pg/ml, p<0.0001), with estimated marginal means of 20.90 pg/ml for Metaberine™ versus 18.40 pg/ml for placebo. Period effect was significant (p=0.0004), whereas sequence and carryover effects were not (p=0.78 and p=0.66, respectively).

Effect on glucose concentration pharmacokinetic parameters

The effects of Metaberine™ and Placebo supplementation on glucose concentration parameters were analyzed using both non-baseline-corrected and baseline-corrected approaches to comprehensively assess postprandial glucose excursions (Figure 3 and Table 4).

For baseline-corrected AUClast, Metaberine™ treatment resulted in values of 96.82±11.64 mg·min/dl at Day 14, representing a 13.5% decrease from baseline. In comparison, placebo showed an increase to 118.35±10.80 mg·min/dl (+5.8% from baseline). Linear mixed model analysis demonstrated an adjusted supplement effect of −10.70 mg·min/dl (SE=1.44, 95% CI: −13.5 to −7.9 mg·min/dl, p<0.0001), with estimated marginal means of 104 mg·min/dl for Metaberine™ compared to 115 mg·min/dl for placebo. Similarly, baseline-corrected Cmax decreased to 69.28±8.54 mg/dl with Metaberine™ (−12.7% from baseline), while placebo increased to 82.75±7.85 mg/dl (+4.6% from baseline). The adjusted treatment difference was −6.61 mg/dl (SE=0.98, 95% CI: −8.5 to −4.7 mg/dl, p<0.0001), with estimated marginal means of 74.3 mg/dl for Metaberine™ versus 80.9 mg/dl for placebo. Period effects were noted for both parameters (AUClast: p=0.056; Cmax: p=0.018), whereas sequence and carryover effects were not significant.

Effect on lipid profile

Metaberine™ supplementation was associated with favorable changes in lipid metabolism (Table 5). Total cholesterol decreased modestly with Metaberine™ from 203.27±21.26 to 200.52±20.21 mg/dl (change −2.75±6.14 mg/dl, p=0.011 within group), while increasing slightly with placebo from 203.69±17.97 to 205.22±17.54 mg/dl (change +1.52±7.99 mg/dl, p=0.260 within group), yielding a significant between-group difference (p=0.013). LDL cholesterol showed a similar pattern: the Metaberine™ group showed a reduction from 136.27±19.42 to 133.61±18.05 mg/dl (change −2.66±5.96 mg/dl, p<0.0001 within group), while the placebo group showed an increase from 132.44±17.16 to 137.58±18.04 mg/dl (change +5.13±7.97 mg/dl, p=0.0004 within group). There were significant difference observed in Metaberine group when compared to Placebo (p<0.0001).

HDL cholesterol increased with Metaberine™ from 44.55±5.78 to 45.81±5.83 mg/dl (change +1.25±1.18 mg/dl, +2.8%, p<0.0001 within group), while decreasing with placebo from 46.52±6.31 to 44.31±6.31 mg/dl (change −2.22±0.79 mg/dl, −4.8%, p<0.0001 within group; p<0.0001 between groups). VLDL showed small decreases in both groups without a between-group difference: Metaberine™ decreased from 22.44±6.60 to 21.11±6.79 mg/dl (change −1.33±1.70 mg/dl, p<0.0001) and placebo decreased from 24.72±6.62 to 23.33±6.53 mg/dl (change −1.38±0.96 mg/dl, p<0.0001), with no significant between-group difference (p=0.865) (Figure 4).

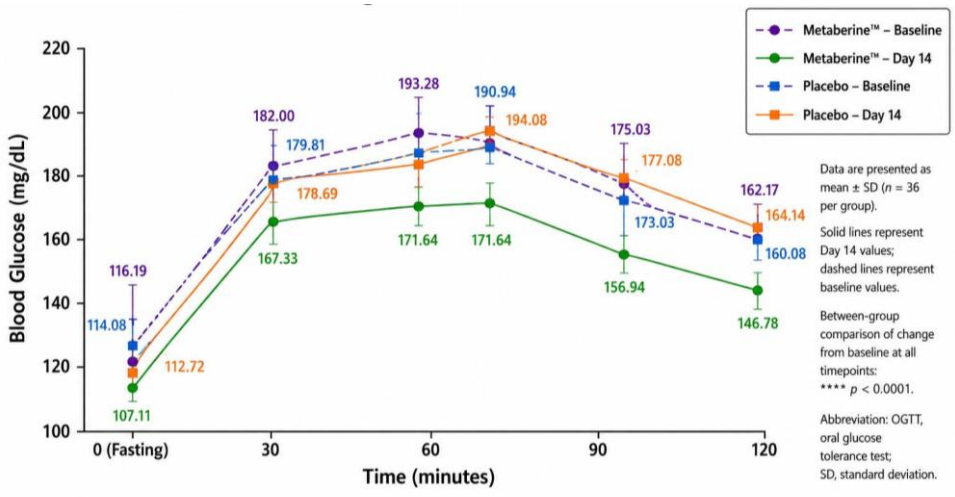

Figure 1: Effect of Metaberine™ on postprandial blood glucose during oral glucose tolerance test.

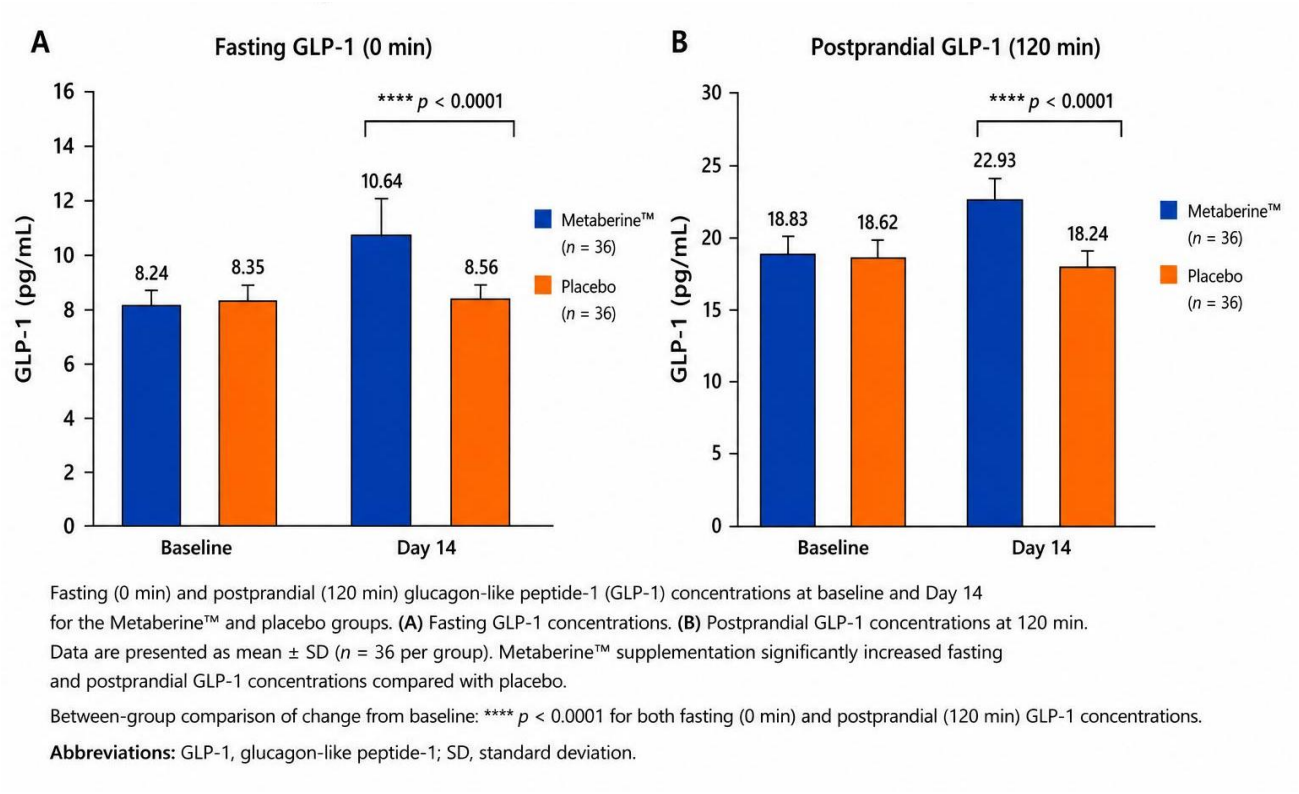

Figure 2: GLP-1 response to Metaberine™ vs placebo.

Baseline-corrected glucose concentration parameters at Day 14 in the Metaberine™ and placebo groups. (A) Area under the concentration–time curve from 0 to 120 minutes (AUClast). (B) Maximum observed glucose concentration (Cmax). Data are presented as mean ± SD (n = 36 per group). Metaberine™ demonstrated significant reductions in AUClast and Cmax compared with placebo. Statistical significance for between-group differences: ****p<0.0001.

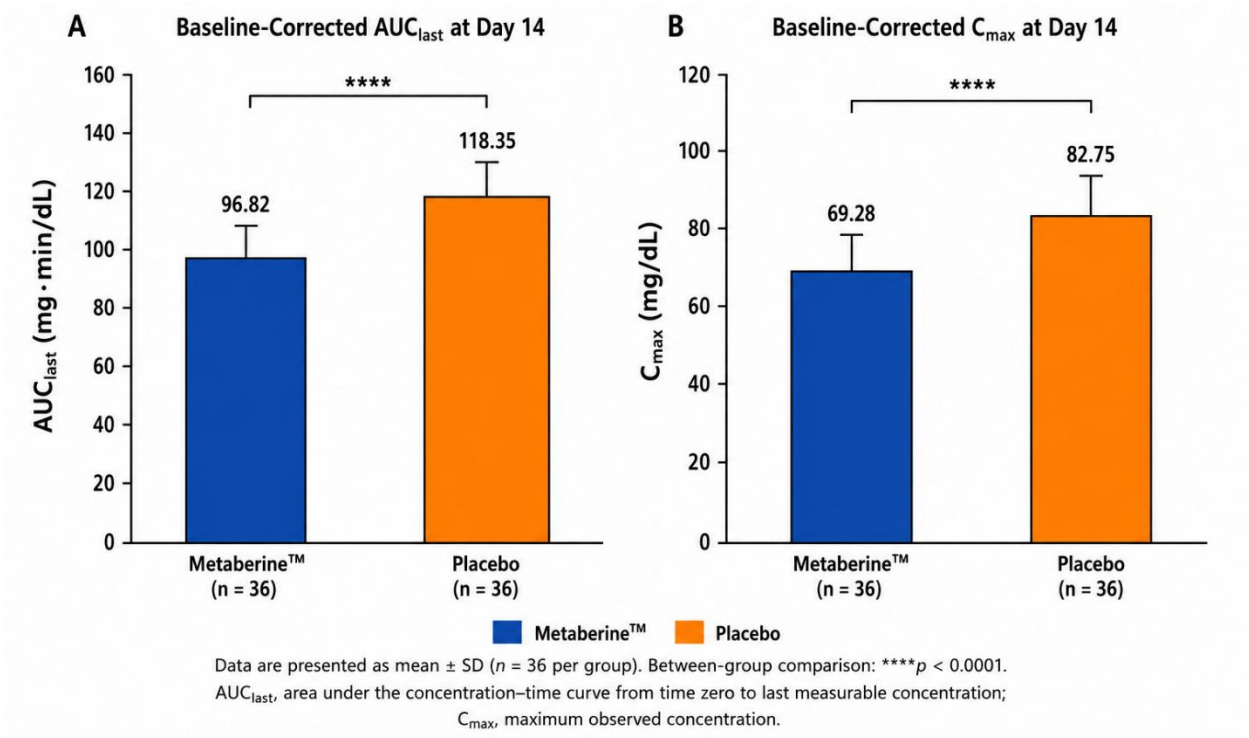

Figure 3: Effect on Metaberine™ on baseline-corrected glucose concentration parameters at day 14.

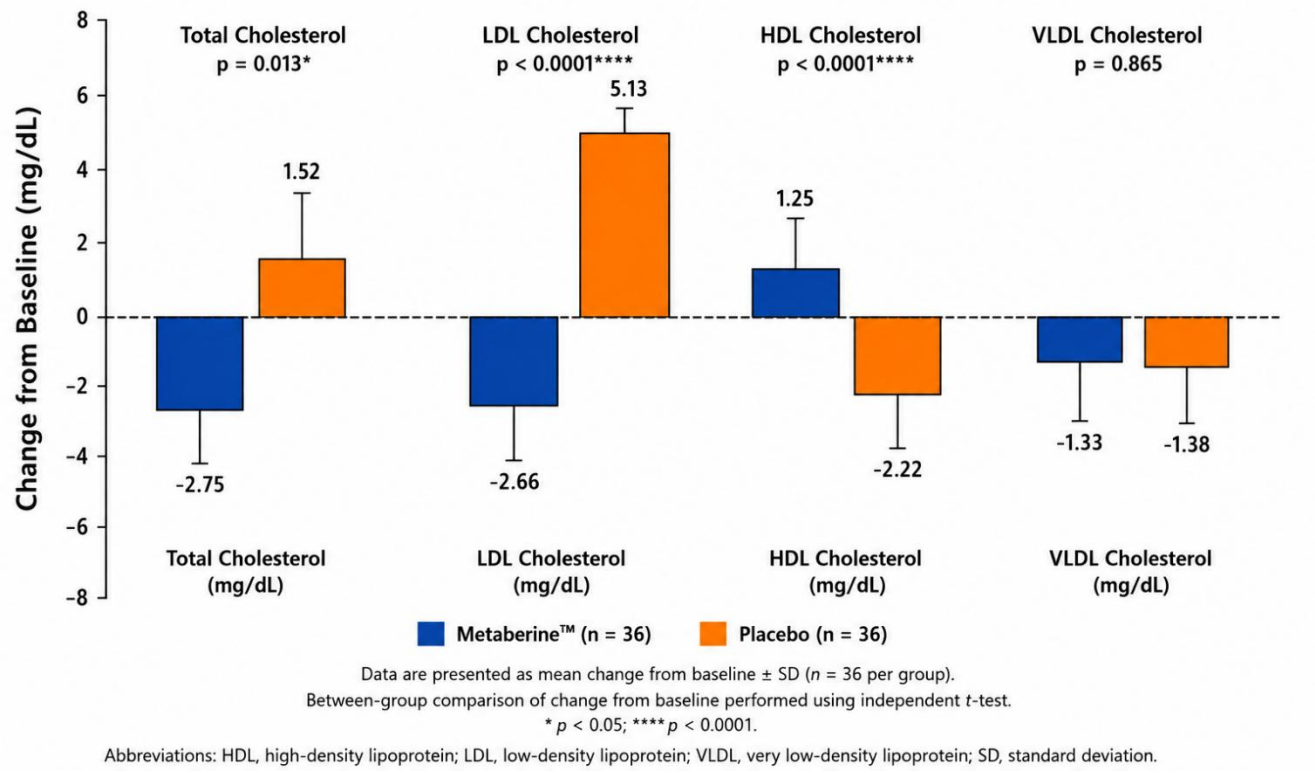

Figure 4: Effect of Metaberine™ on lipid parameters (baseline to day 14).

Table 1: Baseline demographic characteristics.

Study parameter	Sequence A: Metaberine™ → Placebo (n=18)	Sequence B: Placebo → Metaberine™ (n=18)
Male participants, N (%)	10 (55.6)	9 (50.0)
Female participants, N (%)	8 (44.4)	9 (50.0)
Age (years)†	39.92±6.33	39.92±6.33
Height (cm)†	161.94±8.31	161.94±8.31
Weight (kg)†	67.80±9.35	67.85±9.29
BMI (kg/m²)†	25.79±2.58	25.83±2.58

† Data presented as mean±SD.

Effect on anthropometric parameters

There were no significant between-group differences in body weight or BMI at baseline or on day 14 (all p>0.05), indicating comparable anthropometric characteristics between the treatment groups. However, the change from baseline to day 14 showed a significantly smaller increase in both body weight (−0.06±0.45 vs. 0.29±0.35 kg; p<0.001) and BMI (0.02±0.18 vs. 0.11±0.15 kg/m²; p=0.023) in the Metaberine™ group compared with the placebo group.

Safety assessments

Vital signs and clinical laboratory parameters

Vital signs including systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate and temperature remained within normal limits in all participants in both groups throughout the study (Table 7). No clinically significant differences in vital signs were found between the groups at the end of the study. No clinically significant changes were observed in clinical biochemistry (AST, ALT, ALP, BUN, creatinine) or hematology parameters (hemoglobin, RBC, WBC, differential counts, platelets) in either group.

Adverse events

Overall, 8 subjects (22.2%) experienced at least one adverse event (AE), with 2 subjects (11.1%) in the Metaberine group and 6 subjects (33.3%) in the placebo group. A total of 8 adverse events (22.2%) were reported, including 2 events (11.1%) in the Metaberine group and 6 events (33.3%) in the placebo group. Fatigue was reported in 2 participants (5.6%), with 1 participant (5.6%) in each group. Headache was reported in 3 subjects (8.3%), including 1 participant (5.6%) in the Metaberine group and 2 participants (11.1%) in the placebo group. Additionally, one participant each of pain

at the cannula insertion site (2.8%), diarrhea (2.8%) and constipation (2.8%) was reported, all occurring in the placebo group. No other adverse events were observed during the study. All events were transient and resolved without medical intervention. Based on clinical assessment, temporal relationship and participant history, the investigator determined that none of the adverse events were related to the study supplementation. No serious adverse events were reported and no participants discontinued the study due to safety concerns. No clinically significant changes in laboratory parameters or vital signs were observed during the study.

Table 2: Effect of Metaberine™ on postprandial blood glucose during 75 g oral glucose tolerance test.

Time point	Metaberine™ (n=36) Baseline → Day 14	Placebo (n=36) Baseline → Day 14	Between-Group p value‡
0 min (fasting)	116.19±5.24 → 107.11±5.64*	114.08±5.48 → 112.72±6.31	<0.0001*
Change	−9.08±3.52	−1.36±2.71	
30 min	182.00±11.51 → 167.33±12.66*	179.81±10.86 → 178.69±11.13	<0.0001*
Change	−14.67±6.08	−1.11±2.63	
60 min	193.28±6.35 → 171.64±7.77*	190.94±8.16 → 194.08±7.85	<0.0001*
Change	−21.64±5.76	+3.14±4.56	
90 min	175.03±6.11 → 156.94±6.90*	173.03±8.21 → 177.08±6.81	<0.0001*
Change	−18.08±5.34	+4.06±6.36	
120 min	162.17±6.57 → 146.78±7.89*	160.08±7.62 → 164.14±5.95	<0.0001*
Change	−15.39±3.76	+4.06±5.80	

† Data presented as mean±SD. ‡ Between-group comparison of change from baseline performed using independent t-test. $p < 0.05$ versus baseline using paired t-test. Abbreviations: OGTT, oral glucose tolerance test; SD, standard deviation.

Table 3: Effect of Metaberine™ on GLP-1 Response.

Parameter	Metaberine™ (n=36)	Placebo (n=36)	P value‡
GLP-1 Fasting (0 min), pg/ml			
Baseline	8.24±1.48	8.35±1.52	0.761
Day 14	10.64±2.03*	8.56±1.48	<0.0001*
Change	+2.40±1.78	+0.21±0.37	<0.0001*
% Change	+29.1	+2.5	
GLP-1 Postprandial (120 min), pg/ml			
Baseline	18.83±2.71	18.62±1.64	0.699
Day 14	22.93±2.80*	18.24±1.53	<0.0001*
Change	+4.09±1.71	−0.38±0.47	<0.0001*
% Change	+21.7	−2.0	

† Data presented as mean±SD. ‡ Between-group comparisons performed using independent t-test. $p < 0.05$ versus baseline using paired t-test.

Table 4: Effect of Metaberine™ on glucose concentration parameters.

Parameter	Metaberine™ group	Placebo group	P value‡
Non-baseline-corrected			
AUClast–Baseline (mg·min/dl)	344.61±6.81 (n=36)	340.30±10.23 (n=36)	0.039*
AUClast–Day 14 (mg·min/dl)	311.30±8.87 (n=36)	344.02±8.56 (n=36)	<0.0001*
AUCinf–Baseline (mg·min/dl)†	1397.36±331.20 (n=11)	1354.76±285.12 (n=11)	0.750
AUCinf–Day 14 (mg·min/dl)†	1446.60±687.66 (n=13)	1779.84±426.12 (n=9)	0.177
Cmax–Baseline (mg/dl)	195.56±5.12 (n=36)	193.19±7.18 (n=36)	0.113
Cmax–Day 14 (mg/dl)	176.39±6.89 (n=36)	195.47±6.58 (n=36)	<0.0001*
Baseline-corrected			
AUClast–Baseline (mg·min/dl)	111.96±9.48 (n=36)	111.88±8.93 (n=36)	0.969
AUClast–Day 14 (mg·min/dl)	96.82±11.64 (n=36)	118.35±10.80 (n=36)	<0.0001*
AUCinf–Baseline (mg·min/dl)†	200.44±47.38 (n=11)	201.43±32.09 (n=11)	0.955
AUCinf–Day 14 (mg·min/dl)†	185.85±62.81 (n=13)	272.38±50.51 (n=9)	0.002*
Cmax–Baseline (mg/dl)	79.36±7.03 (n=36)	79.11±6.70 (n=36)	0.878
Cmax–Day 14 (mg/dl)	69.28±8.54 (n=36)	82.75±7.85 (n=36)	<0.0001*

† AUCinf was calculable only in participants meeting criteria for reliable terminal phase extrapolation and should be considered exploratory. ‡ Between-group comparisons performed using independent t-test. *$p<0.05$ considered statistically significant.

Table 5: Effect of Metaberine™ on lipid parameters.

Parameter	Metaberine™ group (n=36)	Placebo group (n=36)	P value‡
Total cholesterol (mg/dl)			
Baseline	203.27±21.26	203.69±17.97	0.929
Day 14	200.52±20.21*	205.22±17.54	0.296
Change	−2.75±6.14	+1.52±7.99	0.013*
LDL cholesterol (mg/dl)			
Baseline	136.27±19.42	132.44±17.16	0.378
Day 14	133.61±18.05*	137.58±18.04	0.354
Change	−2.66±5.96	+5.13±7.97	<0.0001*
HDL cholesterol (mg/dl)			
Baseline	44.55±5.78	46.52±6.31	0.171
Day 14	45.81±5.83*	44.31±6.31	0.299
Change	+1.25±1.18	−2.22±0.79	<0.0001*
VLDL cholesterol (mg/dl)			
Baseline	22.44±6.60	24.72±6.62	0.149
Day 14	21.11±6.79*	23.33±6.53	0.162
Change	−1.33±1.70	−1.38±0.96	0.865

† Data presented as mean±SD. ‡ Between-group comparisons of change from baseline performed using independent t-test. $p < 0.05$ versus baseline using paired t-test.

Table 6: Effect of Metaberine™ on anthropometric parameters.

Parameter	Metaberine™ Group (n=36)	Placebo Group (n=36)	p-value‡
Body weight (kg)			
Baseline	67.80±9.35	67.85±9.29	0.987
Day 14	67.74±9.33	68.14±9.27	0.853
Change	−0.06±0.45	+0.29±0.35	0.000*
BMI (kg/m²)			
Baseline	25.79±2.58	25.83±2.58	0.961
Day 14	25.81±2.60	25.94±2.59	0.835
Change	+0.02±0.18	+0.11±0.15	0.023*

† Data presented as mean±SD. ‡ Between-group comparisons of change from baseline performed using independent t-test. $p < 0.05$ versus baseline using paired t-test. Abbreviations: BMI, body mass index; SD, standard deviation.

Table 7: Vital signs summary.

Parameter	Metaberine™ group (n=36) Day 1 → Day 14	Placebo group (n=36) day 1 → day 14
Systolic BP (mmHg)	124.56±7.39 → 125.17±6.98	123.64±7.12 → 124.17±6.73
Diastolic BP (mmHg)	81.47±5.95 → 81.83±6.07	79.58±6.92 → 81.08±6.12
Heart rate (beats/min)	79.39±5.43 → 79.97±5.09	80.33±4.55 → 79.89±5.48
Temperature (°F)	98.18±0.39 → 98.05±0.44	98.08±0.40 → 98.15±0.39

† Data presented as mean±SD. No clinically significant changes in vital signs were observed during the study. Abbreviations: BP, blood pressure; SD, standard deviation.

DISCUSSION

This randomized, double-blind, placebo-controlled, crossover trial demonstrated that Metaberine™, a biooptimised berberine extract developed using BioSOLVE technology, at 200 mg/day significantly improves glycemic control, enhances incretin response and favorably modulates lipid metabolism in healthy adults over a 14-day supplementation period, with excellent safety and tolerability. These findings are preliminary and exploratory in nature given the single-center design, modest sample size and short study duration.

Fasting and postprandial blood glucose

The observed 8% reduction in fasting glucose (−9.08 mg/dl) and 11% reductions in postprandial glucose across OGTT time points compare favorably with prior berberine studies despite the substantially lower dose employed. Published literature shows that standard berberine at 500–1500 mg/day typically achieves fasting glucose reductions of 10–20 mg/dl in populations with

elevated fasting glucose or impaired glucose tolerance.[20,21] A dedicated berberine extract study using 1500 mg/day reported a 21% fasting glucose reduction in individuals with prediabetes a greater absolute effect but at 7.5-fold the dose used in the current study.[22] Importantly, our findings align with meta-analytic data showing berberine reduces fasting glucose with a weighted mean difference of −13.8 mg/dl across multiple randomized controlled trials.[19]

The consistency of effect across all five OGTT time points demonstrates comprehensive attenuation of postprandial hyperglycemic excursions, a glucose exposure pattern independently associated with cardiovascular risk and diabetes progression.[23] The paradoxical worsening of postprandial glucose in the placebo group at later OGTT time points (60–120 minutes) may reflect natural period-to-period variability in glucose tolerance, period effects inherent to crossover designs or regression toward the mean.

GLP-1 response

The 29% increase in fasting GLP-1 and 22% increase in postprandial GLP-1 with Metaberine™ represents a novel and clinically important finding. To our knowledge, only two prior human studies have examined berberine's effects on GLP-1. Zhang et al reported 15–20% increases in GLP-1 with standard berberine 1000 mg/day in type 2 diabetes patients, while a pilot study by Imenshahidi et al and Hosseinzadeh et al showed 12% increases with 900 mg/day berberine in adults with elevated postprandial glucose.[24,25] The findings of robust GLP-1 enhancement at just 200 mg/day substantially exceed these previously reported values and suggest the biooptimised formulation may preferentially enhance incretin-mediated glucose regulation. The magnitude of endogenous GLP-1 enhancement observed is among the largest reported for a natural compound at low dose, which is of significant clinical relevance given the role of GLP-1 in stimulating glucose-dependent insulin secretion, suppressing glucagon, delaying gastric emptying and enhancing peripheral insulin sensitivity.[3] This incretin-modulating effect may contribute substantively to berberine's glucose-lowering efficacy beyond its established AMPK activation and insulin receptor upregulation mechanisms.[7,10]

Glucose pharmacokinetic parameters

The comprehensive assessment of glucose AUC and Cmax parameters provides granular insight into Metaberine™'s glycemic effects. The 13.5% reduction in baseline-corrected AUClast indicates reduced total glucose exposure over the 2-hour post-challenge period a metric closely associated with HbA1c and microvascular complication risk.[26] Similarly, the 12.7% reduction in baseline-corrected Cmax suggests attenuated peak glucose excursions, which independently predict cardiovascular events and diabetes progression beyond mean glucose levels.[27] These pharmacodynamic patterns are consistent with multiple complementary mechanisms: enhanced glucose uptake in skeletal muscle and adipose tissue via AMPK-mediated GLUT4 translocation, reduced hepatic gluconeogenesis, delayed intestinal glucose absorption and incretin-enhanced insulin secretion.[28,29]

Lipid profile

The clinically significant improvements in lipid parameters total cholesterol reduction, LDL-C lowering and HDL-C elevation corroborate prior findings of berberine's pleiotropic metabolic effects.[30] Meta-analyses of berberine in metabolic syndrome and type 2 diabetes report consistent LDL-C reductions of 20–25 mg/dl at doses ≥900 mg/day.[31,32] The observed 2.66 mg/dl LDL reduction with 200 mg/day Metaberine™ over just 14 days is more modest in absolute terms, which is expected given the significantly lower dose and shorter treatment duration; however, it is directionally consistent with the established mechanism and warrants investigation in longer trials. Mechanistically, berberine upregulates hepatic LDL receptor expression via post-transcriptional pathways distinct from statins, enhancing LDL-C clearance and inhibits PCSK9, preventing LDL receptor degradation.[33,34] The simultaneous HDL-C elevation (+2.8%) may reflect enhanced reverse cholesterol transport and apolipoprotein A1 synthesis, as demonstrated in prior berberine investigations.[35]

Safety

The absence of berberine-related adverse events, particularly gastrointestinal effects, represents an important and clinically translatable finding. Standard berberine's dose-limiting gastrointestinal side effects diarrhea (10–30%), abdominal cramping (5–15%), nausea (5–10%) reflect intestinal microbiota modulation and local gut effects at high luminal concentrations.[36,37] By achieving clinical effects at 200 mg/day versus 500 - 1500 mg/day for standard berberine, Metaberine™ minimizes luminal intestinal exposure while enhancing systemic bioavailability. Overall, 8 subjects (22.2%) experienced at least one adverse event, with 2 subjects (11.1%) in the Metaberine group and 6 subjects (33.3%) in the placebo group. No serious adverse events or clinically significant safety signals were observed and comprehensive safety laboratory assessments revealed no concerning signals.

Mechanistic considerations

Results of the current study support the multi-mechanistic actions of berberine: AMPK activation enhancing glucose uptake and fatty acid oxidation; insulin receptor upregulation improving insulin sensitivity; gut microbiota modulation increasing short-chain fatty acid-producing bacteria that enhance GLP-1 secretion; incretin enhancement through direct stimulation of

enteroendocrine L-cells; and improvement in mitochondrial oxidative phosphorylation efficiency.[7,24,34] The biooptimised berberine formulation may preferentially enhance systemic tissue exposure versus gut luminal effects, potentially explaining the favorable safety-efficacy profile observed.

Strengths

Strengths of this study include the rigorous double-blind, placebo-controlled crossover design minimizing between-subject bias, complete participant retention (100%) ensuring robust data integrity, comprehensive glycemic assessments including OGTT, GLP-1 and pharmacodynamic parameters, novel mechanistic data on incretin modulation, inclusion of lipid outcomes and stringent safety monitoring.

Limitations

However, certain limitations should be acknowledged. While the 14-day supplementation period was sufficient to demonstrate early improvements in glycemic control, it is too short to capture longer-term outcomes such as HbA1c changes, which generally require at least 12 weeks or to assess sustained effects on lipid parameters. The sample size, while statistically adequate for primary endpoints, was underpowered for subgroup analyses. The single-center design limits generalizability to other ethnicities and populations. The Day 14 efficacy assessment was conducted 60 minutes after an acute dose; the observed glycemic effects therefore reflect the combined action of 14-day chronic supplementation and an acute pharmacological dose administered prior to the glucose challenge, whose relative contributions cannot be separated. Additionally, the 7-day washout period may be insufficient to fully eliminate berberine's effects on gut microbiota composition and hepatic enzyme expression, which can persist beyond 7 days.[34] No adjustment was made for multiple statistical comparisons; false-positive findings among secondary outcomes cannot be excluded. Dietary intake was not quantitatively assessed.

In summary, Metaberine™ decreased fasting glucose by 8% and postprandial glucose by 11% across all OGTT time points, increased GLP-1 by 22–29%, reduced baseline-corrected AUClast by 13.5% and Cmax by 12.7%, favorably modulated the lipid profile with LDL-C reduction and HDL-C elevation and demonstrated excellent safety without supplement-related adverse events over 14 days in healthy adults at metabolic risk. Further clinical investigation is warranted to assess long-term efficacy, effects on HbA1c and insulin sensitivity and outcomes in broader at-risk populations.

CONCLUSION

This randomized, double-blind, placebo-controlled crossover trial demonstrates that Metaberine™ at 200 mg/day a 5–7-fold dose reduction relative to conventional berberine formulations significantly improves fasting and postprandial glycemic control, substantially enhances endogenous GLP-1 secretion and favorably modulates lipid metabolism in healthy adults at metabolic risk, with 100% participant retention and no supplement-related adverse events. The robust incretin response fasting GLP-1 increased by 29% and postprandial GLP-1 by 22%, exceeding levels previously reported with standard berberine at 4–5 times the dose provides a novel mechanistic dimension connecting low-dose, biooptimised berberine supplementation with endogenous incretin biology. Collectively, these findings advance understanding of the clinical utility of formulation-enhanced berberine by establishing that BioSOLVE technology can overcome the bioavailability barrier that has historically limited berberine's clinical adoption, enabling metabolic benefits at doses that are both effective and well-tolerated. These findings are exploratory and should be confirmed in larger, multicenter, longer-duration trials evaluating HbA1c, insulin sensitivity and cardiovascular risk markers.

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