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A Pilot Crossover Study of Berberine and its Short-Term Effects on Blood Glucose Levels in Healthy Volunteers

Chuck Chang[1], Min Du[1], Kyle Roh[1], Yun Chai Kuo[1], Yiming Zhang[1], Mary Hardy[2], Roland Gahler[3], Julia Solnier[1]*

[1]ISURA, Burnaby, British Columbia, Canada, V3N 4T5
[2]Association of Integrative and Holistic Medicine, San Diego, California, USA
[3]Natural Factors Nutritional Products Ltd, Coquitlam, British Columbia, Canada V3K 6Y2
*Corresponding Author: jsolnier@isura.ca

ABSTRACT

INTRODUCTION: Different berberine preparations were evaluated for their effectiveness on lowering blood glucose in a pilot, open-label, crossover study conducted in healthy adults.

METHODS: Fourteen healthy volunteers of both sexes were recruited, and seven completed all treatments in the study. Study participants ingested one of three berberine preparations containing 500mg of berberine, respectively. A one week wash out period was included between treatments. A control group was included to measure the participants' baseline response to a 75g glucose solution without any treatment, and the following interventions were administered: berberine powder in hard gelatin capsules, berberine in an oil matrix encapsulated in soft-gelatin capsules, and berberine in LipoMicel® matrix encapsulated in soft-gelatin capsules. Blood glucose concentrations in each participant were monitored from pre-dose baseline, before the capsules were ingested, until up to 3 hours after the capsules were ingested.

RESULTS: LipoMicel Berberine treatment led to reduced blood glucose concentrations Area Under Curve (AUC, mean difference: 1.57; 95% CI: 0.021 – 3.12; $P = 0.046$; Cohen's $d = 1.53$) and reduced maximum glucose concentration (Gmax, mean difference: 1.07; 95% CI 0.004 – 2.14; $P = 0.049$; Cohen's $d = 1.52$) compared to the control group when no-treatment was given. No adverse events related to berberine treatments were reported by participants throughout the study period.

CONCLUSIONS: LipoMicel Berberine was effective in lowering blood glucose AUC by 12% after two 500mg doses in 7 participants. Berberine in other formulations may require a longer dosing regimen before blood glucose lowering effects can be demonstrated.

KEYWORDS: Berberine; LipoMicel; blood glucose; human clinical study; micelles; NHP

Introduction

Berberine-rich preparations have been in use in traditional Chinese and Ayurvedic medicines since around 3000 BCE [1], and it has a good safety profile [2–5]. It is a natural phytochemical that can be found in plants such as barberry (*Berberis spp.*), goldenseal (*Hydrastis canadensis*), goldthread (*Coptis spp.*), Oregon grape, phellodendron (*Phellodendron spp.*), heart-leaved moonseed (*Tinospora cordifolia*) and yellowroot (*Xanthorhiza simplicissima*) [6–8]. However, herbal remedies derived from these plants have typically been used to treat gastrointestinal disorders [8] rather than as a remedy for elevated blood glucose levels.

This is most likely owing to the antibacterial and antiviral characteristics of berberine [8–10].

On the other hand, the anti-diabetic effects of berberine were discovered much more recently. In fact, berberine's hypoglycemic effects were studied in a human clinical trial for the first time in 1986 [11]. Since then, more than twenty-eight human studies have been published in which berberine was used as an intervention for treating a range of diseases relating to the metabolic syndrome, cancer, hearth, and neurological diseases [2, 7, 12–15]. In some trials, berberine was used as the sole intervention, whereas in others it was combined with additional oral hypoglycemic medications or lifestyle modifications. According to Liang's comprehensive review and meta-analysis of these studies, there is a definite connection between berberine treatment and lower blood glucose levels [14]. However, one noteworthy and recurring limitation of these studies was that all investigations were conducted in China and only included Chinese participants whose lifestyles, diets, and genetic diversity reflect that specific part of the world. Consequently, generalizability of the results of these studies could be questioned. To address this, the current study was conducted at a Canadian research facility with participants who were subjected to western-focused lifestyle influences and from more diverse backgrounds. Furthermore, treatments in the Chinese studies were rather lengthy. The durations ranged from 14 to 730 days, with more than half of the studies lasting between 30 and 90 days. The extended study periods were due to the low absorption properties of the berberine preparations used [16] and the considerable metabolism of the alkaloid once in circulation [17]. As such, days and even weeks may be required before systemic berberine concentrations accumulate to concentrations that can exert clinically observable effects [1].

Berberine's ability to regulate glucose metabolism has also been extensively researched *in vitro* and *in vivo*. Pang *et al*. reported that berberine likely regulates glucose metabolism through multiple pathways such as increasing insulin sensitivity, activating the adenosine monophosphate-activated protein kinase (AMP-AMPK) pathway, modulating gut microbiota, inhibiting gluconeogenesis in liver, simulating glycolysis in peripheral tissue cells, promoting intestinal glucagon-like protein-1 (GLP-1) secretion, upregulating hepatic low-density lipoprotein receptor mRNA expression, and increasing glucose transport [12]. Furthermore, glycolytic activity has been demonstrated to increase significantly in mouse fibroblasts and myoblasts *in vitro* and in diabetic rats *in vivo* [18] when they are treated with berberine.

However, in order to more fully realize its therapeutic potential, more bioavailable forms of berberine are needed to overcome its poor intestinal absorption and subsequent P-glycoprotein efflux [19]. In this regard, LipoMicel® is a novel delivery system that has improved the bioavailability of flavonoid compounds such as quercetin. It functions by encapsulating the active ingredient(s) in a liquid micelle matrix comprised of natural food-grade ingredients [20]. This study tested the hypothesis that LipoMicel Berberine can reduce blood glucose levels in treatment durations as short as 2 days instead of typical treatment durations of 14 days or longer in past studies. For comparison, two standard products were also tested, one as a powdered berberine in hard-gelatin capsules and the other as berberine encapsulated in an oil-matrix in soft-gelatin capsules.

Methods

Materials

LipoMicel Berberine (LMB) and Powdered Berberine Capsules (PBC, WellbetX, Natural Factors) were provided by Natural Factors (BC, Canada). Berberine in an oil matrix encapsulated in soft-gelatin capsules (BOM, Berberine Glucose Support, Now Foods) was purchased through Amazon. Non-GMO Food Grade glucose was obtained from Univar (BC, Canada). Capillary blood glucose was measured using Contour Next test strips with Contour Next One blood glucose meters (Ascensia Diabetes Care, Switzerland).

Study Design

The open-label pilot study was conducted with a crossover design. Participants were given the interventions with a washout period of seven days or longer between interventions. After the last intervention has been given, more than seven days were allowed to pass before each participant's baseline response was measured again for the next intervention.

Participants

Healthy participants who were 21-years old or older were accepted in the study. Participants must be in good physical condition—non-smokers, not taking any prescribed medication—to be included in the trial. Part of the inclusion criteria also required signing a written informed consent, and a willingness to avoid the consumption of any food and supplements that contain berberine 48 hours before each treatment and during the respective treatment periods.

Participants with any of the following diseases and/or health conditions were excluded: allergy to

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berberine, conditions contraindicated for berberine use, and serious acute or chronic diseases such as liver, kidney or gastrointestinal diseases. These diseases may affect the absorption, metabolism and/or elimination of the treatment. Female participants must not have been pregnant, planning to get pregnant or be breast-feeding. Participants had to complete an online health questionnaire on their medical history upon study enrolment.

Fourteen participants were enrolled, but two dropped out before the first treatment. Out of the remaining twelve participants, seven completed all interventions (Figure 1).

Study Settings

All interventions took place at ISURA's research facilities in Burnaby, BC, Canada. The study took place between November 2021 and March 2022. This coincided with the SARS-CoV-2 Omicron wave where case rates in the local region averaged approximately one hundred cases per 100,000 population per day before the start of the wave and peaked at approximately 2200 per 100,000 population per day in late December. Case rates dropped back down to around 100 per day again by February [21].

The study design took the following factors into account when considering the local health restrictions during the COVID-19 pandemic: safety risks to participants, availability of investigator, staff, equipment, and materials for patient care, drug or device, presence of quarantines, and travel restrictions.

Interventions

Participants were instructed to eat and drink normally for 3 days leading up to the glucose tolerance test. During these 3 days, they could consume an unrestricted diet with no more than 150g of carbohydrates per day. Participants fasted overnight for 8 hours or longer prior to arriving on the morning of Day 1. Then each participant was given a single dose of the intervention to be consumed with a glass of water (250mL) along with a standardized breakfast. Standardized lunch and dinner were also provided.

On the morning of Day 2, participants again arrived after an 8-hour overnight fast. Next, they were given a single dose of the intervention to be consumed with a glass of water (250mL) as with the previous day, but they were instructed not to eat any food. An hour after the intervention was taken (=post-dose), participants were instructed to drink 75 g of glucose dissolved in about 250mL of water and commence the Oral Glucose Tolerance Test.

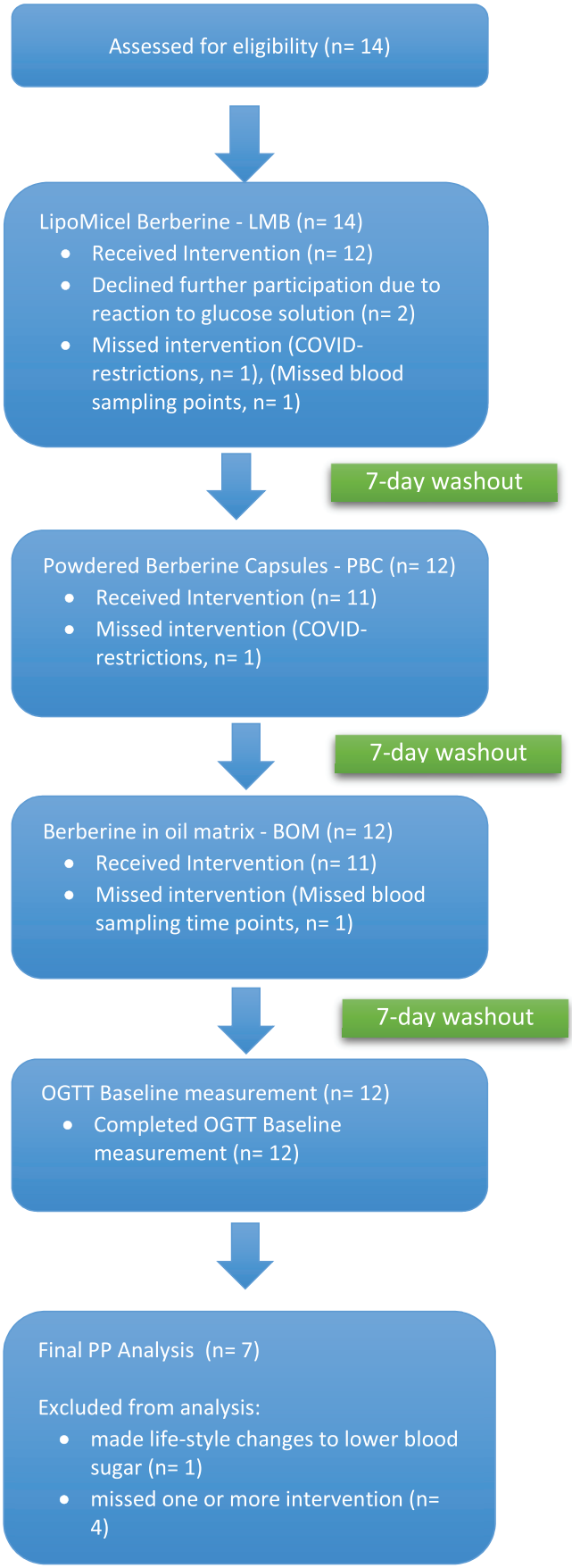

Figure 1. Flow diagram of study design.

The interventions were given in the following sequence with washout periods of at least 7 days in between: LipoMicel® Berberine, Powdered Berberine Capsules, Berberine Softgel Capsules, and then the baseline Oral Glucose Tolerance Test with no intervention (=control) (Figure 1).

Oral Glucose Tolerance Test

Oral Glucose Tolerance Test (OGTT) was performed according to published WHO guidelines [22]. After the first blood glucose measurement, participants ingested seventy-five grams of glucose dissolved in one glass (250mL) of water. Thereafter, capillary blood glucose concentrations were measured at 1.0 hour, 1.5 hours, 2.0 hours, 3.0 hours after ingesting the glucose drink using Contour Next test strips and Contour Next One blood glucose meters.

Glycemic Index (GI)

FAO guidelines were used to calculate the Glycemic Index of the 75g glucose drink using the measured blood glucose levels [23] from the OGTT. Incremental Area Under the Curve (iAUC) was calculated using the trapezoid rule.

Data Analysis

The following blood glucose parameters were evaluated: The time to reach peak plasma concentration (t_{max}), maximum blood glucose concentration (G_{max}), area under the blood glucose concentration curve from 0hr (administration time) to 3hr (AUC) and Glycemic Index (GI).

iAUC represents the incremental amount of glucose that has entered the blood circulation over the first 120 minutes after drinking the glucose solution. Considerations for missing data were made by using the Imputed Mean method.

As for statistical analysis, comparison of parameters between the tested formulations was performed using One-Way Repeated Measures ANOVA with Tukey's HSD post-hoc correction. If sphericity was greater than 0.75, Huynh and Feldt non-sphericity correction (ε) was used, otherwise, the Greenhouse and Geisser non-sphericity correction was used. Data were considered significant at $P < 0.05$. Results are expressed as mean ± standard error of the mean (SEM).

The data analysis for this paper was generated using the Real Statistics Resource Pack software (Release 7.6). Copyright (2013 – 2021) Charles Zaiontz. www.real-statistics.com. This resource pack is an add-on software package for Microsoft Excel.

Results

In this crossover study, all participants were assigned to receive all three interventions in sequential order with washout periods of at least 7 days in between interventions.

Fourteen participants were enrolled to take part in the study (Table 1); two dropped out as the first treatment started because of side effects such as nausea and dizziness after ingesting the glucose solution for the oral glucose tolerance test (OGTT). Thereafter, most of the remaining twelve participants completed the study.

One participant made lifestyle and dietary changes to lower blood glucose levels after the second treatment and was excluded in the Per Protocol (PP) analysis. An additional four participants missed one or more treatments due to pandemic-related restrictions. These participants were also excluded for the PP analysis. Consequently, seven healthy adults of both sexes completed all three treatments of the study (Table 1).

No significance was found between average blood glucose concentrations at any of the measured time points between treatments, but average blood glucose concentrations for the LMB treatment are consistently the lowest of the 3 treatments after the ingesting the treatments (Figure 2).

Adverse Events

No adverse events or gastrointestinal intolerances caused by the treatments were reported throughout the trial.

Lipomicel Berberine Reduces G_{max} and AUC, but not iAUC nor GI during OGTT, PP

When participants were given LipoMicel Berberine (LMB), they had significantly lower blood glucose Area Under Curve values (AUC, mean difference: 1.57;

Table 1. Baseline data of study participants.

	Enrolled Participants (n = 14)	PP Participants (n = 7)
Gender (Males/Females)	6 / 8	4 / 3
Body Mass (kg)	63.27 ± 9.88	64.08 ± 9.32
Age (years)	38 ± 10.3	36.7 ± 9.0
BMI (kg/m2)	22.7 ± 2.53	22.7 ± 2.47
Fasting Blood Glucose (mmol/L)	5.31 ± 0.05	5.38 ± 0.06
Health Status	Non-smokers No serious acute or chronic diseases	Non-smokers No serious acute or chronic diseases

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95% CI: 0.021 – 3.12; $P = 0.046$; Cohen's $d = 1.53$) and maximum blood glucose concentrations (Gmax, mean difference: 1.07; 95% CI 0.004 – 2.14; $P = 0.049$; Cohen's $d = 1.52$) compared to the no-intervention Control (Table 2 and Figure 3). This corresponds to a 7.8% reduction in AUC and a 12% reduction in G_{max} compared to the Control (Table 2).

On the other hand, when participants were given standard Powdered Berberine Capsules (PBC) or Berberine in oil matrix soft-gelatin capsules (BOM), they did not show any significant difference in AUC compared to Control (PBC mean difference: 0.85; 95% CI: –0.69 – 2.40; $P = 0.43$; Cohen's $d = 0.83$, BOM mean difference: 0.85; 95% CI: –0.69 – 2.40; $P = 0.43$; Cohen's $d = 0.83$) or G_{max} (PBC mean difference: 0.41; 95% CI: –0.65 – 1.48; $P = 0.70$; Cohen's $d = 0.59$, BOM mean difference: 0.77; 95% CI: –0.30 – 1.84; $P = 0.21$; Cohen's $d = 1.09$).

For both Incremental Area Under Curve over the period of 120 minutes (iAUC) and Glycemic Index (GI), none of the interventions showed any significant difference compared to the control. However, LipoMicel Berberine trended to a reduction of iAUC (mean difference: 52.9; 95% CI: –8.3 – 114 ; $P = 0.10$; Cohen's $d = 1.31$) and GI (mean difference: 24; 95% CI: –5.6 – 54 ; $P = 0.14$; Cohen's $d = 1.23$).

Discussion

Previously, LipoMicel® has been shown as an effective delivery vehicle for poorly bioavailable phytochemicals such as quercetin [20]. The current study hypothesized that berberine in a similar LipoMicel matrix (LMB) can reduce blood glucose levels in treatment durations as short as 2 days. While small and exploratory, this study observed significant reductions in blood glucose AUC (12% reduction) and G_{max} (7.8%) after participants received two 500mg doses of LipoMicel Berberine.

Notably, the participants in the current research are different from those of earlier study populations in that they were all healthy individuals (Table 1) whereas

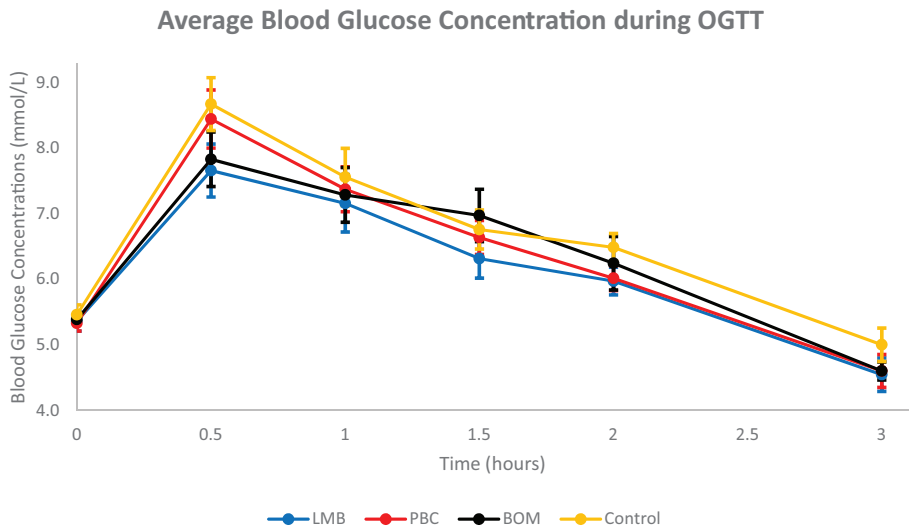

Figure 2. Graph of Average Blood Glucose Concentrations vs. Time during Oral Glucose Tolerance Test (n = 7) of the treatments LipoMicel Berberine (LMB), Powdered Berberine Capsules (PBC), Berberine in oil matrix soft-gelatin capsules (BOM).

Table 2. Results from PP analysis (n = 7). Values with different superscript letters in a column are significant ($p < 0.05$).

Parameters	LMB	PBC	BOM	Control
AUC (mmol·hr·L^{-1})	18.65 ± 0.50^{a}	19.37 ± 0.50^{ab}	19.37 ± 0.50^{ab}	20.22 ± 0.51^{b}
G_{max} (mmol·L^{-1})	7.85 ± 0.38^{a}	8.51 ± 1.09^{ab}	8.16 ± 0.37^{ab}	8.93 ± 1.14^{b}
iAUC (mmol·hr·L^{-1})	161 ± 24	204 ± 23	191 ± 33	214 ± 21
GI	76 ± 12	99 ± 11	87 ± 11	100 ± 0

LMB: LipoMicel Berberine; PBC: Powdered Berberine Capsules; BOM: Berberine in oil matrix soft-gelatin capsules.

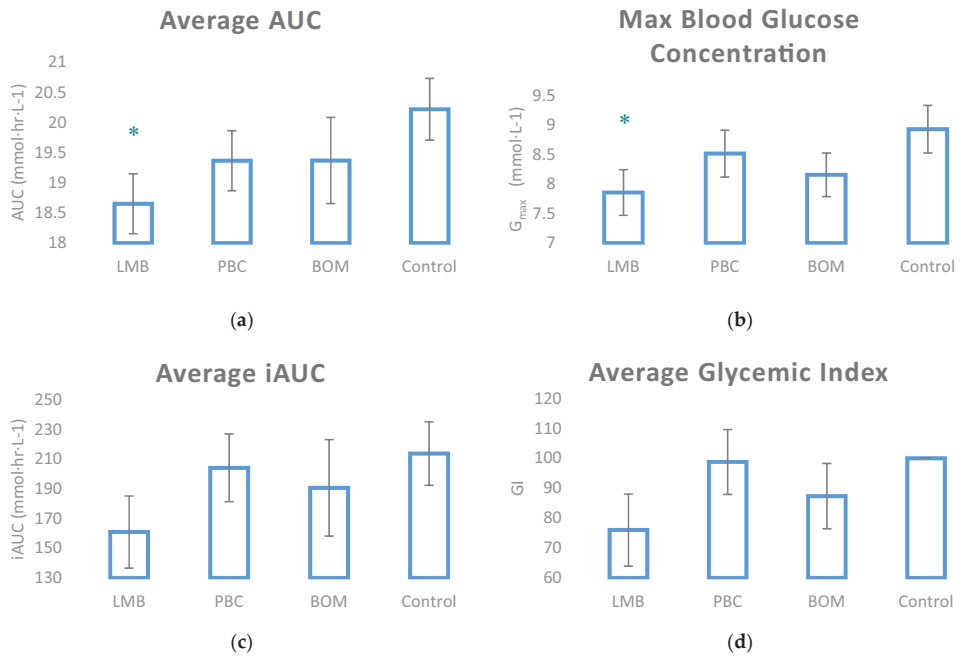

Figure 3. Graphs of blood glucose related parameters during the Oral Glucose Tolerance Test (n = 7). (a) Average AUC of blood glucose concentrations over 3 hours during each intervention: LipoMicel Berberine (LMB), Powdered Berberine Capsules (PBC), Berberine in oil matrix soft-gelatin capsules (BOM). LMB is significantly lower than Control ($p = 0.046$) (b) Maximum blood glucose concentrations during the 3 hours of OGTT for each intervention. LMB is significantly lower than Control ($p = 0.049$) (c) iAUC over 120 minutes for each intervention. LMB is not significantly lower than Control ($p = 0.10$) (d) Average Glycemic Index of the 75 g glucose solution during the OGTT for each intervention. LMB is not significantly lower than Control ($p = 0.14$). * $p < 0.05$

earlier studies include individuals with diabetes or hyperglycemia [14]. The earlier Chinese research also did not account for smokers. However, a 1999 survey reported that 34.1% of the Chinese population smoke [24]. Because smoking can also lower fasting insulin levels and temporarily raise blood sugar levels after an oral glucose challenge [25, 26], this study, in contrast, only included non-smokers in order to guarantee more consistent blood glucose measurements.

Some insights into the pharmacological action of berberine can be gleaned by comparing the profiles of average glucose concentrations during oral glucose challenge for the 4 groups (Figure 2). While the between groups data at each sampling time point were not significant on their own, LMG treatment consistently showed lower average blood glucose levels after oral ingestion of the intervention at Time 0, which led to a significantly lower blood glucose AUC compared to Control (Figure 2 and Table 2). This finding is consistent with previous reports that berberine can reduce Post Prandial Glucose (PPG) in diabetic patients [14, 27], and the significantly lower G_{max} values in the LMB group is further evidence of this berberine property in healthy individuals. Interestingly, the current work adds that berberine does not appear to lower Fasting Blood Glucose (FBG) levels of individuals with normal FBG (Table 1), whereas previous work reported that berberine lowers FBG of diabetic individuals [14]. This has positive implications for the use of berberine as a preventative treatment for blood sugar control since decreases in PPG was reported to be a more sensitive and specific predictor of glycemic control compared to FBG [28].

On the other hand, the lack of significance when comparing iAUC and GI of LMB against control indicates that the effect of berberine is observed over a longer period (180 minutes for AUC) rather than the shorter durations used to measure iAUC and GI (120 minutes). This observation also supports previous findings that regular berberine dosage forms with low bioavailability requires longer duration to see clinically significant effects [12, 14, 15]. But possibly, a larger study with higher statistical power could also find statistical significance in lower iAUC and GI values.

To address the need to for long treatment durations to observe berberine's pharmacological effects, a recent human study used dihydroberberine, a derivative synthesized through borohydride reduction of berberine, to overcome the challenge of poor bioavailability [16, 29].

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While dihydroberberine is a normal metabolite of berberine, and has even been shown to inhibit mitochondrial respiration *in vitro* [30, 31], the study failed to demonstrate any reduction in blood glucose levels compared to a placebo control group. The study used a dosage regimen similar to the current study [16]. But surprisingly, participants achieved much higher blood concentrations of berberine compared to standard berberine, yet the increased berberine concentration in the blood was not accompanied by expected reductions in blood glucose levels [16]. Perhaps, precisely because dihydroberberine is a metabolite of berberine, its presence could reduce or inhibit the conversion of berberine into other metabolites with greater biological activity. A future study that compares of metabolite profiles from oral intake of berberine versus dihydroberberine could shed more light on the difference in the reported results.

This study has several limitations. Foremost are the non-randomization design as well as the small sample size. While randomization is a tool to reduce potential bias due to systematic errors [32], significant bias remains in smaller trials with less than 1000 participants. It has been reported that cross-over designs such as the one used in the current study may be a more effective alternative to mitigate bias since they reduce the variance of estimates [33]. The use of commercial off-the-shelf glucose meters and test strips have been shown to provide good clinical accuracy compared to a laboratory comparator, and this also minimizes potential measurement bias [34].

The unintentionally small sample size can be attributed to a high dropout rate resulting from governmental restrictions during the COVID-19 pandemic. At one time, travelling more than 20km was restricted to essential travel if it means crossing a health region. These restrictions prevented previously enrolled study participants from taking part in the study unless they lived within the same health region as the study center. And while none of the participants tested positive for COVID-19 during the course of this study, some had developed flu-like symptoms that restricted them from further participation. This resulted in more missed treatments and dropouts. However, these problems are by no means unique to the current study since other researchers have also reported increased dropouts for trials conducted during the pandemic [35, 36].

Another contribution to dropouts was that the glucose solution in Oral Glucose Tolerance Test was not well tolerated. While serious side effects from OGTT are rare, some have reported feeling nauseated, sweaty, or lightheaded after drinking the glucose solution [37]. It has been suggested that the solution should be standardized [38], and in the current study, pure glucose was freshly dissolved in water by participants just before consumption. Still, two participants decided the unpleasant sensations were too much for them to continue. Future studies may require flavouring the solution to make it more palatable.

A separate pandemic related limitation is that blood insulin levels could not be measured due to restricted availability of non-essential health services at contract laboratories. Measuring blood insulin levels during the study could determine whether the observed anti-hyperglycemic effects can be attributed to a change in basal insulin levels [39]. Future studies could address this by measuring basal insulin levels pre- and post- treatment. Nonetheless, the findings of this small-scale pilot study may be a precursor for larger investigations and more sophisticated RCTs looking into the (long-term) effects of berberine on blood sugar levels when encapsulated in a delivery system such as LipoMicel.

Conclusions

This small, exploratory study demonstrates with blood glucose concentration measurements in an Oral Glucose Tolerance Tests that LipoMicel® Berberine reduces blood glucose AUC by 7.8% and G_{max} by 12% compared to no-intervention control. Surprisingly, while previous studies on berberine typically require daily berberine doses over a period of two weeks or longer before clinical effects are measurable, results from LipoMicel Berberine are observed after just two days of taking a 500mg LipoMicel Berberine dose per day. Future studies utilizing larger sample sizes and broader ethnic representations are warranted to verify the significance of current observations and to more thoroughly examine the physiological relevance of LipoMicel Berberine in humans. Moreover, subsequent studies focusing on participants who have glucose-related disorders (such as diabetes and obesity) also would be valuable, where any pharmacological benefits of LipoMicel Berberine could be elucidated.

List of Abbreviations Used

AMP-AMPK: Adenosine Monophosphate-Activated Protein Kinase
AMP: Adenosine Monophosphate
ANOVA: Analysis of Variance
ATP: Adenosine Triphosphate
AUC: Area Under Curve of Blood Glucose Concentrations, Observed Over 3 Hours

BOM: Berberine in Oil Matrix Soft-Gelatin Capsule
COVID-19: Coronavirus Disease of 2019
CI: Confidence Interval
ERK: Extracellular Signal-Regulated Kinases
FAO: The Food and Agricultural Organization of the United Nations
FBG: Fasting Blood Glucose
GI: Glycemic Index
GLP-1: Glucagon-Like Protein-1
Gmax: Maximum Blood Glucose Concentration
GMO: Genetically Modified Organism
iAUC: Incremental AUC of Blood Glucose Concentrations, Observed Over 120 Minutes.
hr: Hour
L: Liter
LMB: LipoMicel® Berberine
MAPK: Mitogen-Activated Protein Kinases
mmol: Millimolar
mRNA: Messenger Ribonucleic Acid
NHP: Natural Health Product
OGTT: Oral Glucose Tolerance Test
PBC: Powdered Berberine Capsule (non-oil matrix)
PP: Per Protocol
PPG: Post Prandial Glucose
RNA: Ribonucleic Acid
WHO: World Health Organization

Conflicts of Interest

CC, KR, MD, and YCK, and JS are employees of Isura and have no other conflicts. MH and ML receive consulting fees from the Factors Group of Companies. RG is the owner of the Factors Group of Companies. ISURA is a not-for-profit independent organization.

Ethics Approval and/or Participant Consent

The study protocol was approved by the Canadian SHIELD Ethics Review Board (Ontario, Canada) (OHRP Registration IORG0003491; FDA Registration IRB00004157; Approval letter ID 2021-0, date of approval: June 15, 2021). The study was conducted in accordance with the ethical standards as set forth in the Helsinki Declaration of 1975. All participants provided their written informed consent before participation in this study.

Authors' Contributions

CC, KR, MD, YCK, YMZ, JS: contributed equally to this work.

CC: made contributions to the design of the study, collected and analysed data, drafted the manuscript, and gave final approval of the version to be published.

KR, MD, YCK, YMZ: conducted experiments, collected and analyzed data, and contributed to drafting the manuscript—review and editing, and gave final approval of the version to be published.

MH: contributed to drafting the manuscript – review and editing

RG: contributed to the design of the experiments and to drafting the manuscript – review and editing

JS: made contributions to the design of the study, collected and analysed data, critically reviewed the manuscript, and gave final approval of the version to be published.

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LipoMicel® Matrix is the registered trademark of Natural Factors Group.

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