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Review Article

Berberine dosing for lowering blood glucose: a model-based meta-analysis

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Abstract: This study used a non-linear mixed-effects Emax model to analyze quantitatively the longitudinal time-course profile, onset characteristics, and maximum efficacy of berberine (BBR) using data from 28 clinical trials (64 arms, 2,669 subjects). Study heterogeneity was controlled by covariate screening and estimating between-study variability. The model revealed that baseline fasting blood glucose (FBG) exponentially increased the theoretical E_{max}, while body mass index (BMI) prolonged the half-maximal onset time (ET_{50}) as a power function. Monte Carlo simulations for typical patients (baseline FBG: 7 mmol/L; BMI: 26 kg/m^2) showed that after 90 days of treatment, FBG decreased by 1.02 mmol/L in the metformin (MET) group and 0.793 mmol/L (11.33%) in the berberine (BBR) group, whereas the placebo effect was negligible (0.01 mmol/L). The 90-day efficacy of BBR was 77.76% of that of MET. Point-estimate simulations suggested a rapid early treatment response; however, sensitivity analysis across the bootstrap range of ET_{50} indicated substantial uncertainty in the exact onset trajectory. Higher baseline FBG markedly enhanced drug efficacy. Notably, in obese populations (BMI: 32 kg/m^2), the efficacy of most single drugs drastically dropped to 0.5%-1.2%, in which the BBR & others combination group demonstrated the highest efficacy (1.18 mmol/L, 1.69%). In conclusion, BBR exhibits a comparable, rapid onset pattern to MET, with its efficacy tightly driven by baseline glycemia. While BBR monotherapy shows limitations in obese patients, BBR-inclusive combinations offer superior glycemic control, providing essential quantitative insight for clinical guidelines.

Keywords: Berberine, diabetes mellitus, model-based meta-analysis, metformin, blood glucose

Introduction

The global incidence of blood glucose irregularities has progressively increased annually. Diabetes mellitus (DM) is the quintessential malady within this spectrum, and as of 2019, the population with DM has increased to a staggering 463 million individuals. Projections predict anincrease to 700 million diabetes patients globally by the year 2045, with type 2 diabetes mellitus (T2DM) accounting for 90% of cases [1]. Hyperglycemia, a common condition in which glucose metabolism is affected, is intricately linked to anomalies in diverse physiologic systems, wherein etiological factors include hyperthyroidism, hypercortisolism, and hepatitis, among others. Previous studies revealed insulin resistance, pancreatic β-cell dysfunction, and the overexpression of inflammatory responses as concomitant phenomena in subjects with and animal models of hyperglycemia. It was additionally demonstrated that the interaction of the aforementioned factors can increase blood glucose levels to the extent where hyperglycemia ultimately develops [2]. To date, insulin, metformin, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, and glucagon-like peptide-1 (GLP-1) receptor agonists have been verified as representative hypoglycemic medications [3]. Nevertheless, the majority of hypoglycemic medications have side effects, including hepatotoxicity, nephrotoxicity,

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or cardiovascular toxicity, and most of the curative agents are costly, leading to certain restrictions in treatment [4].

Berberine (BBR), an isoquinoline alkaloid derived from Coptis chinensis, offers the advantages of affordability, minimal side effects, and widespread clinical applicability [5, 6]. Numerous studies have demonstrated its noteworthy hypoglycemic effects, including increased insulin sensitivity, improved insulin resistance, enhanced GLP-1 secretion in the small intestine, and inhibition of liver gluconeogenesis [7-9]. Additionally, BBR reduces sugar absorption by intestinal cells, mitigates oxidative stress and inflammation, and regulates changes in the intestinal microenvironment, collectively improving the condition of individuals with hyperglycemia [10, 11].

Despite these findings, there is a lack of large-scale investigations regarding the role of BBR in glycemic regulation, and previous studies have yielded inconsistent outcomes. This study aimed to address this gap by performing a meticulous evaluation of BBR interventions in individuals with hyperglycemia through the application of model-based meta-analysis (MBMA). MBMA, which employs pharmacologic modelling, explicitly incorporates treatment duration and other covariates, thereby mitigating between-study heterogeneity. Our study employed MBMA to perform a comprehensive quantitative analysis of the hypoglycemic efficacy and temporal dynamics of BBR in diabetes patients. Furthermore, we endeavored to compare the effectiveness of BBR with that of other pharmacological agents, thereby providing more cogent evidence for its judicious clinical use. This research was preregistered with PROSPERO (CRD42022313775) and meticulously adhered to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Materials and methods

Search strategies

A literature search was conducted for pertinent clinical trials published up to June 30, 2022, using the public databases PubMed and Embase. The search keywords included clinical signs, medication names, and indications. The logical operators “AND” and “OR” were used to link keywords that belonged to different categories or were related, and the detailed search strategies are provided in Table S1 of supplementary materials.

Inclusion and exclusion criteria

Inclusion criteria: (1) Studies enrolling patients with chronic primary T2DM characterized by impaired glucose regulation, metabolic syndrome, or other chronic primary disorders diagnosed according to any clinical or diagnostic criteria, as well as patients with Cushing’s syndrome, polycystic ovary syndrome, and other conditions causing secondary glucose abnormalities; (2) Clinical trials that included at least one intervention arm and met at least one of the following requirements: 1) administration of BBR at different doses; or 2) inclusion of a combination drug group or drug intervention containing BBR that satisfied both of the following conditions: (I) the supplement complex did not contain any other medications with hypoglycemic effects; and (II) the dose and frequency of BBR could be calculated accurately; (3) Studies in which the negative control group comprised patients awaiting treatment, receiving nonpharmacological interventions, or receiving a placebo, and studies in which the positive control group comprised patients receiving metformin (MET) monotherapy regimens alone or nonpharmacological treatments combined with metformin; (4) Studies reporting fasting blood glucose (FBG) data, including at a minimum baseline data and data from at least one additional follow-up visit; and (5) Randomized controlled trials.

Exclusion criteria: (1) experimental studies, case reports, literature reviews, systematic reviews or meta-analyses, and conference abstracts; (2) studies including patients with other hereditary blood glucose regulation disorders, such as type 1 diabetes mellitus (T1DM); (3) studies in which the trial arm contained a sample size of less than 10; (4) studies in which additional drugs were used in the non-BBR intervention group; (5) studies with a lack of relevant endpoint data; and (6) studies with unclear data, or studies that failed to extract effective data.

Intervention classification

To ensure mutually exclusive and clinically meaningful group boundaries, the treatment

groups included in the study were strictly divided into five groups based on their active pharmaceutical ingredients and dosage forms:

Berberine (BBR) Group: Clinical trials evaluating berberine as a monotherapy.

BBR & others Group: Co-administration designs where berberine was combined with other separate chemical or herbal hypoglycemic drugs.

Berberine-containing drugs (C-BBR) Group: Fixed-dose combination (FDC) formulations or traditional patent medicines that inherently contain berberine within their botanical matrix.

Metformin (MET) Group: Metformin monotherapy arms, serving as the primary active reference standard.

Drugs without berberine components (N-BBR) Group: Non-berberine active control groups consisting of standard chemical hypoglycemic agents (excluding Metformin) to evaluate the relative efficacy profile of BBR against broader anti-diabetic options.

Data extraction

Microsoft Excel (version 2016) was used to extract the following information from the included literature: (1) basic information: authors, year of publication, clinical trial number, DOI number; (2) trial design characteristics: trial drug, administered dose, frequency of administration, duration of treatment, and sample size; (3) characteristics of subjects: disease progression, age, height, weight, BMI, proportion of males (baseline characteristics); and (4) clinical trial results: duration of trial visits and corresponding FBG levels. Moreover, Engauge Digitizer (version 11.1) was used to extract graphical data from the literature. Data extraction was carried out independently by two researchers, with a third researcher intervening to determine whether there were discrepancies in the extracted data.

Literature quality assessment

Literature quality was assessed by two researchers using the Cochrane risk of bias tool, and disagreements were resolved after discussion with a third researcher. The assessments included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective reporting bias and other important biases.

Model establishment

Structural model: Exploratory analysis of the time-varying FBG data revealed that the change in the patients' FBG levels from baseline over time showed a rapid decline followed by a gradual plateau. This was consistent with the classical pharmacodynamic model, the E_{max} model (Equation 1) [12, 13], which states that a drug's efficacy increases gradually and eventually converges to a plateau as time passes. The Emax model is the classical empirical model and the most commonly used empirical model in pharmacodynamics to describe nonlinear relationships [13].

$$E_{i,j} = \frac{E_{max,i} + Time_{i,j}}{ET_{50,i} + Time_{i,j}} \quad (1)$$

In Equation 1, $E_{i,j}$ is the efficacy of the i^{th} drug or placebo group at time point j. $E_{max,i}$ is the theoretical maximum efficacy of the i^{th} drug or placebo arm, and $ET_{50,i}$ is the time required to reach half of $E_{max,i}$, reflecting the onset of the drug or placebo.

Covariate model: Covariate modelling can be used for screening potential factors that influence clinical efficacy. The covariates examined in this study included publication year, daily administered dose, patient age, patient BMI, proportion of males, and baseline FBG level. To ensure model stability and result accuracy, a covariate was excluded if the missing data rate was greater than or equal to 30%; for covariates with a missing data rate less than 30%, the missing values were imputed using the median of the remaining data. Although variables such as daily dose and duration of diabetes were considered clinically relevant, they were excluded from the final model. Daily dose was excluded because it failed to meet the statistical significance threshold during the stepwise selection ($\Delta OFV < 3.84$). The duration of diabetes was excluded prior to screening due to a missing data rate exceeding 30% across the trials, which could otherwise introduce substantial bias to the parameter estimation.

The way a covariate was introduced into the model depended on the data type of the covariate. Equation 2 displayed the form in which categorical variables were introduced, and Equations 3-5 displayed the forms in which continuous variables were introduced.

$$P_i=P_{pop}\times(1+COV_i\times\theta_{COV}) \quad (2)$$

$$P_i=P_{pop}\times(1+(COV_i-COV_{median})\times\theta_{COV}) \quad (3)$$

$$P_i=P_{pop}\times e^{(COV_i-COV_{median})\times\theta_{COV}} \quad (4)$$

$$P_i=P_{pop}\times(COV_i/COV_{median})^{\theta_{COV}} \quad (5)$$

In Equations 2-5, P_i is the individual value of the model parameter of the i^{th} drug or placebo group, and P_{pop} represents the population typical value of the model parameter P when the value of the categorical covariate is 0 or the value of the continuous covariate is equal to COV_{median}. θ_{cov} is the correction coefficient of the covariate on the model parameter. COV_i represents the value of the covariate in the i^{th} study, and cov_{median} is the median of the covariate in the data set.

The stepwise method was used to screen the covariates introduced into the model. First, the effect of covariates on model parameters was examined by introducing covariates one by one, and if the objective function value of the model decreased by more than 3.84 (χ^2; $P < 0.05$; df = 1), the covariates were considered to have a significant effect on the parameters. Subsequently, the possibility of incorrect covariates was checked by removing the introduced covariates one by one, and if the value of the model's objective function increased by less than 6.63 (χ^2; $P < 0.01$, df = 1), the covariates were considered to have a statistically insignificant effect on the parameters. The above method allowed for the identification of covariates that were ultimately introduced into the model [14, 15].

Random effects model: Differences in drug effects between studies can be represented by interstudy variability (η). In this study, additive and exponential models were chosen to describe the intertrial variability (Equations 6 and 7):

$$P_i=P_{typical}+\eta_i \quad (6)$$

$$P_i=P_{typical}\times e^{\eta_i} \quad (7)$$

In Equations 6 and 7, P_i is the value of the model parameter of the i^{th} drug or placebo group, $P_{typical}$ is the population-typical value of the model parameter, and η_i is the variation in the model parameter between studies, conforming to a normal distribution with a mean of 0 and a variance of ω^2 [16].

Unexplained variation is categorized as residual error (ε), and this study described residual variation by an additive model (Equation 8):

$$Y_{observe,i,j} = Y_{predict,i,j} + \frac{\varepsilon_{i,j}}{\sqrt{N_{i,j}}} \quad (8)$$

In Equation 8, $Y_{observe,\ i,\ j}$ represents the observed efficacy value at time point j of trial group i, and $Y_{predict,\ i,\ j}$ represents the predicted efficacy value at time point j of the i^{th} drug or placebo group. $\varepsilon_{i,\ j}$ is the residual for group i at time point j, which needs to be weighted by the inverse of the square root of the sample size ($N_{i,\ j}$). For instance, it is assumed that the larger the sample is, the smaller the residuals are. $\varepsilon_{i,\ j}$ follows a normal distribution with mean of 0 and a variance of σ^2 [17].

Model evaluations

In this study, goodness-of-fit graphs were used to assess model fit. Comparisons between observations and population predictions allow for accurate assessment of random effects; comparisons between observations and individual predictions help accurately assess residuals. The relationship between conditionally weighted residuals and population prediction values as well as the relationship between conditionally weighted residuals and observed time points both enable an assessment of the homogeneity and independence of residual distributions. All the above assessments of the estimates can be shown graphically [18]. The bootstrap method was used to assess the stability of the model. A total of 1000 repeated samples from the original data set and 1000 new data sets were used to estimate model parameters, and then the median and 95% confidence intervals of the model parameters estimated from the original data set were compared to those estimated from the new data set. A closer value indicated that the model was more stable and less influenced by individual studies [19]. A visual predictive check can assess the predictive performance of the

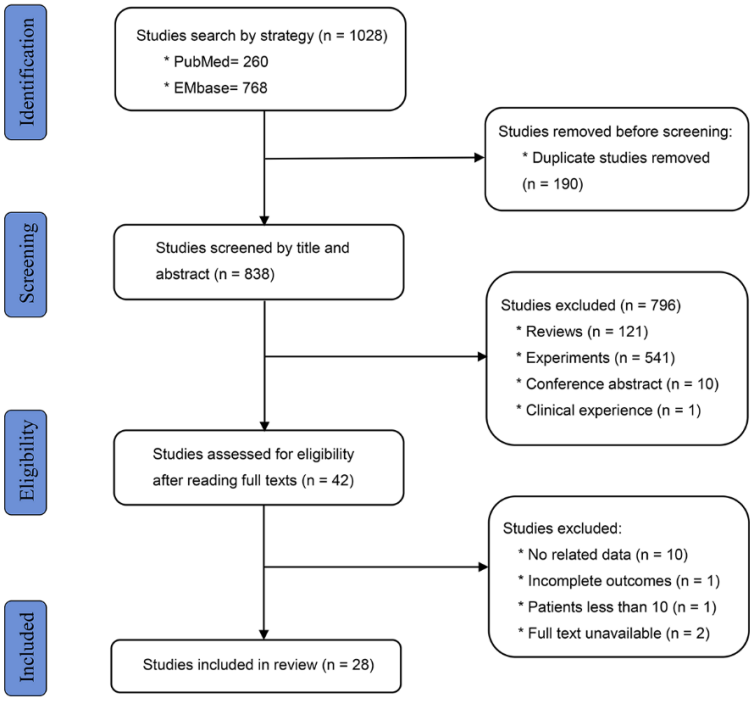


Figure 1. Flow chart of literature screening.

model by comparing the extent to which the model's predicted values match the observed values. The method was simulated 1000 times by the Monte Carlo method to obtain 95% confidence intervals for the individual predictions and compared with the observations [20].

Model simulations

Model parameter estimates and their standard errors were used to simulate changes in FBG levels over time in patients receiving treatment. Based on the results of model parameter estimation and 10,000 Monte Carlo simulations, typical values of patients' FBG changes with treatment duration at different covariate levels and their 95% confidence intervals were obtained. In addition, for treatment groups using different drugs, the model was used to compute empirical Bayesian posterior estimates of the included trials in each group. After adjusting for the different covariate effects of each trial, the Bayesian estimation results of the included trials in each group were pooled and analyzed using meta-analysis to obtain the corresponding mean values of the population parameter estimates and the corresponding standard errors for that group. Based on the respective population parameter estimates of each group, the typical values of the changes in patients' FBG levels with treatment duration and their 95% confidence intervals for different drugs at different levels of covariates were obtained by 10,000 Monte Carlo simulations to compare the differences in efficacy between different drug treatment groups. Differences in the efficacy between the placebo and different medication treatments were compared on the basis of the model's simulated efficacy to assess more appropriate treatment options in various situations.

Software

Microsoft Excel version 2016 and Engauge Digitizer version 11.1 were used for data extraction and processing. NONMEN 7.4 was used for model building and fitting. RevMan 5.4 was used to assess the quality of the studies. R 4.1.1 and RStudio 1.3.1093 were used for data sorting, model evaluation, model simulation, meta-analysis and graphing.

Results

Characteristics of the included studies

A total of 28 studies with 64 trial arms totaling 2669 subjects were ultimately included, and the literature screening process is shown in **Figure 1**. A total of 19 studies were included in the placebo group (N = 847), and 28 studies were included in the drug group (N = 1822). The drug arms were divided into 5 categories: 6 studies were included in the MET group (N = 233), 14 studies were included in the BBR group (N = 628), 4 studies were included in the combined berberine and other berberine-free ingredients (BBR & others) group (N = 161), 13 studies were included in the berberine-containing drugs (C-BBR) group (N = 550), and 5 studies were included in the drugs without berberine components (N-BBR) group (N = 250). The included studies were published between 2008 and 2021, and the duration of the clini-

Table 1. Summary of included literature

	All	Drugs	Placebo	MET	BBR	BBR & Others	C-BBR	N-BBR
Number of trials/arms	28/64	28/45	19/19	6/6	14/14	4/4	13/16	5/5
Total sample size	2669	1822	847	233	628	161	550	250
Sample size per arm, Median (Min, Max)	40.5 (9, 100)	32 (12, 100)	44 (9, 99)	28 (16, 100)	49 (12, 100)	46 (12, 57)	30 (15, 81)	57 (12, 100)
Baseline, mmol/L, Median (Min, Max)	6.385 (4.55, 10.9)	6.75 (4.67, 10.9)	5.2 (4.55, 7.88)	8.76 (5.1, 10.9)	6.43 (4.97, 10.63)	8.01 (5.5, 9.8)	7.775 (4.67, 8.8)	6.4 (5.5, 9.1)
Dose, g/d, Median (Min, Max)	1.176 (0.004, 2.4)	1.176 (0.004, 2.4)	-	1.5 (1.176, 1.5)	1.25 (0.6, 1.5)	2.35 (1.2, 2.4)	1.176 (0.1573, 1.5)	0.8 (0.004, 1.4)
Age, year, Median (Min, Max)	50.68 (25.74, 67.85)	50.72 (25.74, 67.85)	50.64 (26.75, 58.3)	41.63 (26.03, 66.9)	45.355 (25.74, 57)	51.68 (46.8, 57)	53.525 (30.7, 67.85)	53 (44.8, 54.16)
BMI, kg/m^2, Median (Min, Max)	26.75 (22.6, 36.1)	27.3 (22.9, 34.7)	26.6 (22.6, 36.1)	26.6 (24, 34.7)	26.6 (24.3, 34.2)	26.65 (25.2, 29)	28.25 (22.9, 30.53)	26.6 (25.25, 31.5)
Gender, male%, Median (Min, Max)	51.06 (0, 85)	51.06 (0, 85)	50 (0, 75)	51.06 (0, 85)	51.06 (0, 68.97)	44.83 (16.67, 55.1)	51.335 (42.5, 75)	50 (42.11, 59)
Year, Median (Min, Max)	2015 (2008, 2021)	2015 (2008, 2021)	2015 (2008, 2021)	2012 (2008, 2021)	2015 (2008, 2021)	2019 (2008, 2021)	2015 (2011, 2021)	2018 (2010, 2021)

Table 2. Final model parameter estimates and bootstrap results

Parameter	Mean Estimate	RSE (%)	Bootstrap Median	Bootstrap 95% CI
E_{max}, typical, mmol/L	0.36	16.3	0.37	0.23 to 0.49
ET_{50}, typical, day	3.13	65.2	3.02	0.1 to 21.76
Baseline on E_{max}, mmol/L	0.55	9.2	0.54	0.43 to 0.7
BMI on ET_{50}, kg/m^2	26.5	29.8	25.3	1.1 to 51.62
ω (E_{max})	0.39	11.3	0.38	0.28 to 0.48
ω (ET_{50})	3.44	38.1	3.45	0.78 to 8.06
σ	0.56	19.2	0.55	0.33 to 0.76

cal trials ranged from 42 to 360 days. The mean age of the included patients ranged from 25.74 to 67.85 years, the BMI ranged from 22.6 to 36.1 kg/m^2. Summary information on the included studies is shown in **Table 1**. The results of the literature quality assessment are shown in Figures S1 and S2.

Modelling and evaluations

In this study, we found that the changes in the FBG levels from baseline in the patients in the included studies showed a time-dependent decrease that was well described by the E_{max} model. Therefore, we used the change in the FBG level from baseline as an observation and quantitatively analyzed the relationship between the onset time of drug therapy and the reduction in FBG levels by constructing an E_{max} model.

After applying six covariates, including year of publication, daily dose administered, patient age, patient BMI, proportion of males, and baseline FBG level, it was found that the baseline FBG level had a significant effect on the E_{max} parameter, and patient BMI had a significant effect on the ET_{50} parameter. The final covariate relationships are shown in Equations 9 and 10.

$$E_{max,i}=E_{max,typical}\times e^{(Baseline-6.38)\times 0.554} \quad (9)$$

$$ET_{50,i} = ET_{50,typical} \times (\frac{BMI}{26.6})^{26.5} \quad (10)$$

The relationships between the above covariates and the model parameters indicated that as the baseline FBG level of the patients increased, the theoretical maximum efficacy of drug therapy in reducing FBG levels increased exponentially; that is, the greater the baseline FBG level of the patients was, the more pronounced the effect of the drug was. As the patients' BMIs increased, the time required for drug therapy to reduce the FBG level to half of the theoretical maximum efficacy increased in the form of a power function, which indicated that the greater the BMI of the patient was, the longer the onset of drug action. The final model, constructed after the introducing baseline FBG and BMI, and its parameter estimates and standard errors are shown in **Table 2**.

The final goodness-of-fit graph (Figure S3) showed that the observations and population predictions were evenly distributed on both sides of the diagonal line, and the fitted regression lines almost coincided with the diagonal line. The conditional weighted residuals were all less than 6 and evenly distributed on both sides of the zero line, and the fitted regression lines of the conditional weighted residuals versus population predictions and the conditional weighted residuals versus onset time almost coincided with the 0-scale line. The above results indicated that the model's interindividual variation and residual distribution were accurately estimated, the residuals were uniformly and independently distributed, and the model fit the observed data well without obvious bias. As presented in **Table 2**, the estimated ET_{50} parameter exhibited a relatively high standard error (RSE: 65.2%; estimate: 3.13 days), which primary reflects sparse early sampling time-points across historical trials. This relatively high standard error reflects the inherent data sparsity in sampling early onset time-points across historical clinical trials. To further quantify the impact of uncertainty in ET_{50} on the predicted time-course profile, a scenario-based sensitivity analysis was performed using the lower limit of the bootstrap 95% CI, the point estimate, and the upper limit of the bootstrap 95% CI for ET_{50} (0.10, 3.13, and 21.76 days,

Table 3. Parameter estimates and standard errors (SE) for each treatment

Treatment	E_{max}	SE (E_{max})	ET_{50}	SE (ET_{50})
Placebo	0.057	0.059	21.370	13.442
MET	0.764	0.086	7.98	4.685
BBR	0.6	0.114	7.486	6.849
BBR & Others	0.307	0.1	1.786	0.788
C-BBR	0.447	0.053	5.68	2.59
N-BBR	0.239	0.113	5.865	5.613

respectively), while holding the remaining model parameters constant (Table S2). At day 10, the predicted proportions of Emax achieved were 99.0%, 76.2%, and 31.5%, respectively. By day 90, the corresponding proportions were 99.9%, 96.6%, and 80.5%, respectively. These results indicate that uncertainty in ET_{50} substantially affects predictions of the early treatment trajectory, whereas longer-term efficacy predictions are comparatively less sensitive to this parameter uncertainty. Nevertheless, the bootstrap method achieved a success rate of 91% in 1,000 fits, and the median parameter distributions (E_{max}: 0.37 mmol/L; ET_{50}: 3.02 days) closely aligned with the final model estimates. These findings support the overall reproducibility of the model estimates, although the wide confidence interval for ET_{50} indicates that the precise timing of early treatment onset remains uncertain. This robust bootstrap agreement confirms that the overall dynamic trend and parameter stability were less affected by individual study leverage. The visual predictive check plot (Figure S4) showed that the median change in the FBG level from the baseline value obtained by the model simulations and its 95% confidence interval covered almost all the observed values, which indicated that the results obtained by the model simulation were consistent with the observational data and that the model had good predictive performance.

Comparison of the efficacy of different drug treatments

To compare the differences in efficacy between the placebo group and each drug treatment group, a meta-analysis was conducted after adjusting for the different covariate effects in each trial. This analysis was carried out for each model to obtain parameter estimates by empirical Bayesian posterior estimation, and the means and standard errors of the group parameter estimates corresponding to each group were obtained (**Table 3**). The MET group had the best efficacy in terms of theoretical maximum efficacy, followed by the BBR group, while the efficacy of the placebo group was almost negligible; in terms of time to onset of action, the fastest onset of action was observed for the BBR & others group, while there was no significant difference in the time of onset of action between the MET and BBR groups, and the slowest onset of action was observed for the placebo group.

Based on the parameter estimates gained from the empirical Bayesian posterior estimates, 1,000 simulations were subsequently performed using the Monte Carlo method, and the typical efficacy and 95% confidence intervals for FBG over time were finally obtained for the placebo and other drug groups. **Table 4** and **Figure 2** show the typical efficacy and 95% confidence intervals when the patients had a baseline FBG level of 7 mmol/L and a BMI of 26 kg/m^2, and **Figure 3** shows the results of comparing typical efficacy values when the patients with the above characteristics were treated with the placebo and each drug. In the placebo group, the FBG level decreased by 0.034 mmol/L (0.49%) after 10 days of treatment and by 0.01 mmol/L (0.14%) after 90 days of treatment, suggesting that the efficacy of the placebo was almost negligible. The MET group experienced a decrease in the FBG level of 0.74 mmol/L (10.57%) after 10 days of treatment and a decrease of 1.02 mmol/L after 90 days of treatment. In the BBR group, the FBG level decreased by 0.574 mmol/L (8.2%) after 10 days of treatment and by 0.793 mmol/L (11.33%) after 90 days of treatment; in the BBR & others group, the FBG level decreased by 0.388 mmol/L (5.54%) after 10 days of treatment and by 0.424 mmol/L (6.06%) after 90 days of treatment; in the C-BBR group, the FBG level decreased by 0.474 mmol/L (6.77%) after 10 days of treatment and by 0.605 mmol/L (8.64%) after 90 days of treatment; and in the N-BBR group, the FBG level decreased by 0.238 mmol/L (3.4%) after 10 days of treatment and 0.322 mmol/L (4.6%) after 90 days of treatment. The results of the drug group simulations indicated that the patients achieved at least 70% of the effi-

Table 4. Typical values and confidence intervals for the efficacy of each treatment over time (Median, 95% CI, mmol/L)

TIME (day)	Placebo	MET	BBR	BBR & Others	C-BBR	N-BBR
1	6.994 (6.969, 7.007)	6.800 (6.536, 6.929)	6.837 (6.472, 6.970)	6.789 (6.592, 6.929)	6.847 (6.712, 6.931)	6.928 (6.709, 6.996)
2	6.990 (6.946, 7.013)	6.663 (6.339, 6.867)	6.730 (6.322, 6.942)	6.720 (6.492, 6.9)	6.755 (6.593, 6.876)	6.883 (6.622, 6.993)
3	6.985 (6.929, 7.018)	6.564 (6.230, 6.812)	6.654 (6.242, 6.916)	6.683 (6.446, 6.887)	6.694 (6.528, 6.833)	6.853 (6.580, 6.991)
4	6.982 (6.916, 7.022)	6.490 (6.159, 6.764)	6.597 (6.188, 6.892)	6.661 (6.418, 6.878)	6.649 (6.485, 6.798)	6.830 (6.55, 6.989)
5	6.978 (6.905, 7.025)	6.430 (6.106, 6.723)	6.552 (6.155, 6.870)	6.646 (6.399, 6.872)	6.616 (6.454, 6.768)	6.813 (6.529, 6.988)
10	6.966 (6.871, 7.038)	6.260 (5.973, 6.568)	6.426 (6.06, 6.779)	6.612 (6.354, 6.857)	6.526 (6.376, 6.677)	6.762 (6.475, 6.983)
15	6.958 (6.850, 7.046)	6.178 (5.909, 6.471)	6.363 (6.017, 6.718)	6.599 (6.337, 6.852)	6.484 (6.339, 6.632)	6.738 (6.448, 6.982)
20	6.952 (6.839, 7.051)	6.130 (5.873, 6.408)	6.327 (5.989, 6.673)	6.592 (6.326, 6.85)	6.461 (6.317, 6.605)	6.723 (6.433, 6.98)
30	6.945 (6.821, 7.058)	6.073 (5.83, 6.329)	6.282 (5.955, 6.614)	6.585 (6.316, 6.848)	6.434 (6.29, 6.576)	6.705 (6.411, 6.979)
40	6.94 (6.810, 7.063)	6.041 (5.804, 6.286)	6.257 (5.934, 6.578)	6.582 (6.310, 6.847)	6.420 (6.277, 6.562)	6.695 (6.402, 6.978)
75	6.932 (6.792, 7.070)	5.990 (5.759, 6.225)	6.217 (5.900, 6.529)	6.577 (6.302, 6.845)	6.399 (6.256, 6.541)	6.681 (6.381, 6.977)
90	6.930 (6.787, 7.072)	5.980 (5.749, 6.214)	6.207 (5.893, 6.520)	6.576 (6.301, 6.845)	6.395 (6.251, 6.537)	6.678 (6.377, 6.976)

Notes: Data are presented as predicted median fasting blood glucose (FBG, mmol/L) and 95% confidence intervals (CI); Absolute reduction at Day 90 is calculated as Baseline (7.00 mmol/L) -Predicted FBG. (e.g., MET reduction: 1.02 mmol/L [14.57%]; BBR reduction: 0.79 mmol/L [11.33%]).

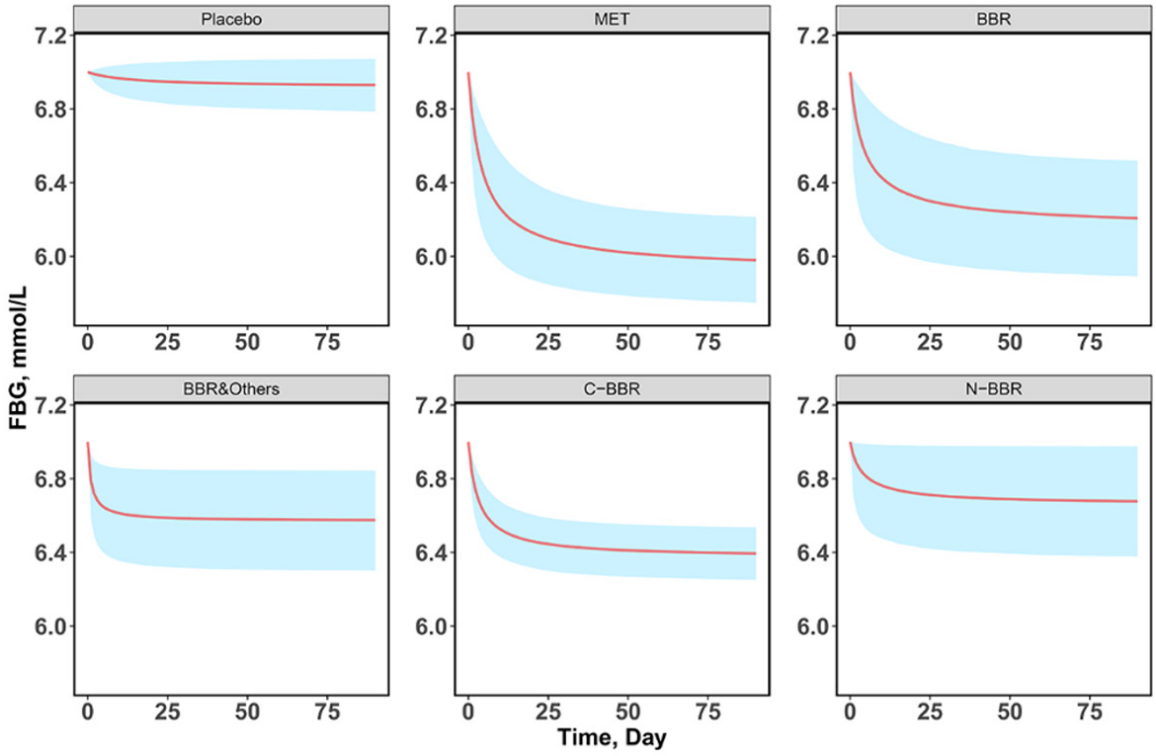


Figure 2. Typical values and 95% CIs for changes in placebo and each drug's efficacy over treatment time (baseline FBG value = 7 mmol/L, BMI value = 26). Visual curves represent continuous model predictions; exact numerical values at key time-points are explicitly provided in **Table 4**.

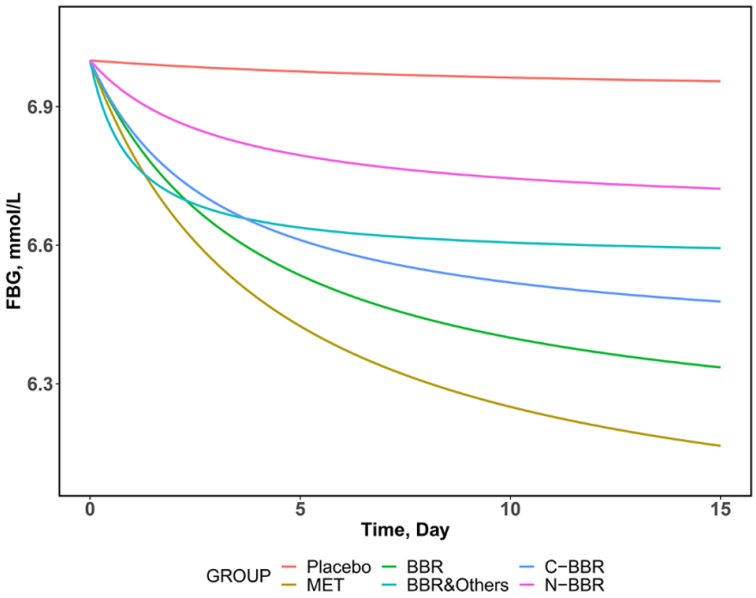


Figure 3. Comparison of typical values for placebo and each drug's efficacy over treatment time (baseline FBG value = 7 mmol/L, BMI value = 26).

cacy after 10 days of treatment that they had achieved after 90 days of treatment. The efficacy of the BBR group after 90 days of treatment was approximately 77.75% of that of the MET group; the efficacy of BBR & others group was approximately 41.57% of that of the MET group; the efficacy of the C-BBR group was approximately 59.3% of that of the MET group; and the efficacy of the N-BBR group was approximately 31.57% of that of the MET group.

Comparison of efficacy at different baseline levels

Table 5 and **Figure 4** show the results of the comparison of typical efficacy values when patients had a BMI of 26 kg/m^2 and received treatment for 90 days. When patients had baseline concentrations of 5, 6.5, and 8 mmol/L, the efficacy was 0.023 mmol/L

Table 5. Typical efficacy for each treatment of different baseline and BMI levels (mmol/L)

	Placebo	MET	BBR	BBR & Others	C-BBR	N-BBR
BASELINE						
5	4.977	4.661	4.733	4.859	4.799	4.893
5.5	5.469	5.052	5.148	5.313	5.235	5.358
6	5.959	5.41	5.535	5.754	5.65	5.813
6.5	6.446	5.721	5.887	6.175	6.038	6.253
7	6.929	5.973	6.191	6.572	6.391	6.675
7.5	7.406	6.145	6.433	6.935	6.696	7.071
8	7.876	6.212	6.592	7.255	6.94	7.434
BMI						
18	6.92	5.923	6.154	6.567	6.37	6.663
20	6.92	5.923	6.154	6.567	6.37	6.663
22	6.92	5.924	6.155	6.567	6.37	6.663
24	6.921	5.929	6.159	6.568	6.372	6.664
26	6.929	5.973	6.191	6.572	6.391	6.675
28	6.958	6.199	6.361	6.598	6.494	6.731
30	6.988	6.658	6.719	6.708	6.751	6.869
32	6.998	6.916	6.93	6.882	6.933	6.965
34	6.999	6.982	6.985	6.97	6.985	6.992
36	7	6.996	6.997	6.993	6.997	6.998

Notes: Values in **Table 5** are rounded to three decimal places. Therefore, very small differences between adjacent BMI levels may not be apparent in the tabulated values, whereas **Figure 5** was generated from the unrounded continuous model predictions.

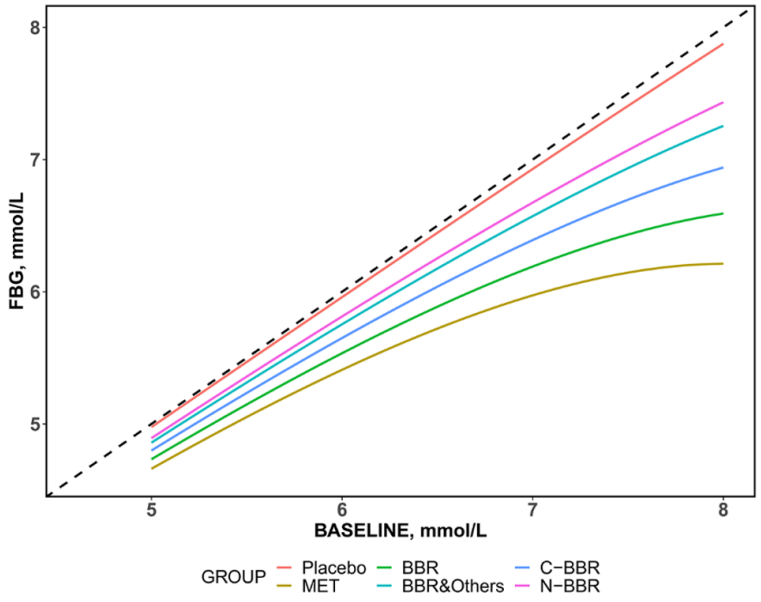


Figure 4. Comparison of typical values for placebo and each drug's efficacy with baseline changes in patient FBG (BMI value = 26, treatment time = 90 d).

(0.46%), 0.054 mmol/L (0.83%), and 0.124 mmol/L (1.55%) in the placebo group; in the MET group, the efficacy values were 0.339 mmol/L (6.78%), 0.779 mmol/L (11.98%), and 1.788 mmol/L (22.35%), respectively; in the BBR group, the efficacy values were 0.267 mmol/L (5.34%), 0.613 mmol/L (9.43%), and 1.408 mmol/L (17.6%), respectively; in the BBR & others group, the efficacy values were 0.141 mmol/L (2.82%), 0.325 mmol/L (5%), and 0.745 mmol/L (9.31%), respectively; in the C-BBR group, the efficacy values were 0.201 mmol/L (4.02%), 0.462 mmol/L (7.1%), and 1.06 mmol/L (13.25%), respectively; and in the N-BBR group, the efficacy values were 0.107 mmol/L (2.14%), 0.247 mmol/L (3.8%), and 0.566 mmol/L (7.08%), respectively. The above results indicated that the efficacy increased 1.77-fold when the patients' FBG concentration increased from 5 mmol/L to 6.5 mmol/L and by 1.87-fold when the patients' FBG concentration increased from 6.5 mmol/L to 8 mmol/L.

Comparison of treatment efficacy at different BMIs

The BMI scenario simulations covered values from 18 to 36 kg/m^2. Predictions at the upper end of this range should be interpreted cautiously because fewer trial-level observations were available at very high BMI values. Since the relationship between the time required for drug therapy to reduce the FBG level to half of the theoretical maximum efficacy and the BMI took the form of a power function, differences in the BMI could significantly affect the time to drug onset of action. Especially for patients with a higher BMI, the clinical treatment period was significantly different from that for patients with a lower BMI. Comparison

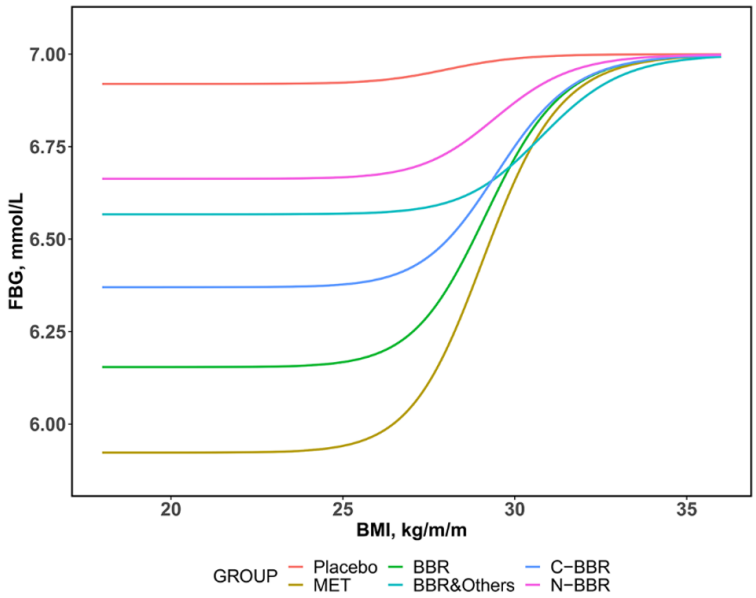


Figure 5. Comparison of typical values for placebo and each drug's efficacy with changes in patient BMI (baseline FBG value = 7 mmol/L, treatment time = 90 d).

of the efficacy of various types of drugs in patients with different BMIs may show large differences and should be performed separately. Additionally, a formal interaction analysis was conducted to test whether the covariate effects of baseline FBG and BMI on the model parameters (Emax and ET50) were interdependent. The interaction term was statistically non-significant ($\Delta OFV < 3.84$, $P > 0.05$), indicating that baseline glycemic levels and body mass index act as independent predictors of the therapeutic trajectory of berberine.

Table 5 and **Figure 5** show the results of the comparison of typical values of efficacy when patients had a baseline FBG concentration of 7 mmol/L and received treatment for 90 days. When patients had a BMI of 20, 26, or 32 kg/m^2, the efficacy values in the placebo group were 0.08 mmol/L (1.14%), 0.071 mmol/L (1.01%), and 0.002 mmol/L (0.03%), respectively; the efficacy values in the MET group were 1.077 mmol/L (15.39%), 1.027 mmol/L (14.67%), and 0.084 mmol/L (1.2%), respectively; the efficacy values in the BBR group were 0.846 mmol/L (12.09%), 0.809 mmol/L (11.56%), and 0.07 mmol/L (1%), respectively; the efficacy values in the BBR & others group were 0.433 mmol/L (6.19%), 0.428 mmol/L (6.11%), and 0.118 mmol/L (1.69%), respectively; the efficacy values in the C-BBR group were 0.63 mmol/L (9%), 0.609 mmol/L (8.7%), and 0.067 mmol/L (0.96%), respectively; and the efficacy values in the N-BBR group were 0.337 mmol/L (4.81%), 0.325 mmol/L (4.64%), and 0.035 mmol/L (0.5%), respectively. The above results showed that the distribution of efficacy of each drug group was 4.81%-15.39% when a patient's BMI was 20 kg/m^2, and 4.64%-14.67% when a patient's BMI was 26 kg/m^2, which did not show significant changes compared to a BMI of 22 kg/m^2. However, when a patient's BMI was 32 kg/m^2, the distribution of the efficacy of each drug group was 0.5%-1.69%, and at these values, the efficacy of the BBR & others group was the best, and the difference in efficacy between the other drug groups was very small.

Discussion

To accurately illustrate the impact of BBR interventions on hyperglycemia, we employed FBG levels as an analytical metric to gauge the effectiveness of BBR in treating diabetes in this study. FBG, a globally recognized predictive criterion for the diagnosis and clinical treatment of DM, has also served as a prominent indicator in previous research on the hypoglycemic effect of BBR [21-23]. Glycated hemoglobin (HbA1c), despite its equal importance in the development of DM, was not accounted for in this analysis due to the lack of research.

Extensive investigations have confirmed that the glucose-lowering effects of BBR are comparable to those of MET [24]. Promoting GLP-1 secretion is one of the main mechanisms of BBR in the treatment of hyperglycemia [25]. By enhancing the intestinal flora composition and increasing the abundance of bacteria that produce short-chain fatty acids (SCFAs), BBR hinders the progression from prediabetes to T2DM, reducing blood glucose levels in T2DM rats [26]. By increasing the relative abundance of microbial communities containing *Myco-*

bacterium anisopliae and the family Clostridiaceae in rats, BBR facilitates the conversion of cholic acid (CA) to secondary bile acids, specifically deoxycholic acid (DCA) [27]. Furthermore, BBR was shown to increase the production of GLP-1, activate G protein-coupled bile acid receptor 5 in intestinal L cells, and improve diseases related to glucose metabolism [28]. In addition, BBR can control mitochondrial stress by inhibiting ATP overproduction, thereby protecting intestinal L cells and promoting GLP-1 secretion [29]. Additionally, BBR inhibits mitochondrial glucose oxidation in L6 myoblasts, increases the adenosine monophosphate/adenosine triphosphate (AMP/ATP) ratio, promotes AMP-activated protein kinase (AMPK) and p38MAPK phosphorylation, and regulates the secretion of GLP-1 through the AMPK/p38MAPK/NF-κB/IL-6 pathway to exert a hypoglycemic effect [30-35].

Other conceivable mechanisms of the glucose-lowering action of BBR include the following: increased expression of the insulin receptor, subsequent activation of AMPK, and receptor tyrosine kinase (RTK)-mediated activation of the phosphoinositide 3-kinase (PI3K) pathway, thereby augmenting glucose transport and peripheral tissue utilization [36]; upregulation of protein kinase C, which increases the expression of insulin receptor mRNA; activation of GLUT1-mediated glucose uptake in 3T3-L1 adipocytes via the AMPK pathway [37]; and inhibition of multiple transcription factors, which in turn inhibit phosphoenolpyruvate carboxykinase and glucose-6-phosphatase, which are rate-limiting enzymes [38]. By reducing gluconeogenesis and enhancing glucose absorption, transport, and utilization, BBR lowers blood glucose levels. Additionally, BBR increases the expression of pancreatic and duodenal homeobox 1 (PDX-1) in pancreatic tissue and stimulates insulin production. BBR also improves this condition by inhibiting macrophage phagocytosis and secretion of the inflammatory factor TNF-α, among other pathways [39]. Therefore, a comparative quantitative analysis of the efficacy of BBR with different treatment regimens has important clinical value and can be used as a reference standard for the design of future clinical trials, providing the possibility of different interpretations of clinical trial results.

By developing a pharmacodynamic model, we were able to analyze the efficacy of berberine on lowering blood glucose levels and how it differs from other medications in this investigation. BBR had a greater glucose-lowering effect than C-BBR and N-BBR but a slightly lower effect than the traditional diabetes medication (MET) after controlling for the effects of baseline FBG levels and BMI. The theoretical maximum effect value (E_{max}) of BBR also approaches 80% of that of MET. The difference in efficacy between the two, however, is dynamic and varies with the baseline FBG value and BMI since the real efficacy is influenced by the two factors previously discussed. For patients with a lower baseline FBG level or a higher BMI, the difference was minimal. Therefore, considering its lower side effects, BBR may represent a treatment option for such patients, although this finding requires prospective clinical validation.

In addition to the efficacy of BBR and MET, the model results illustrate that the efficacy of other treatments is also dependent on the covariates of baseline FBG levels and BMI. These variables reflect the pathological basis and physiologic characteristics of patients' islet function, insulin levels, and glycogen metabolism, which, in turn, influence the treatment efficacy and prognosis of diabetes patients [40]. BMI, which is intricately linked with metabolic syndrome, including DM, not only directly affects insulin sensitivity but also indirectly interferes with normal insulin metabolism through oxidative stress and the immune response stemming from abnormalities in body fat metabolism, ultimately affecting the efficacy of glucose-lowering medication [41, 42]. Therefore, these two factors should be considered when choosing treatment.

The relatively high uncertainty surrounding ET_{50} should be considered when interpreting the early time-course predictions. Although the point estimate suggested a relatively rapid onset of glucose-lowering efficacy, the RSE of ET_{50} was 65.2% and the bootstrap 95% CI ranged from 0.10 to 21.76 days, indicating substantial uncertainty in the precise timing of onset. In the scenario-based sensitivity analysis, the proportion of E_{max} achieved by day 10 ranged from 31.5% to 99.0%, whereas by day 90 it ranged from 80.5% to 99.9%. These find-

ings indicate that uncertainty in ET_{50} has a greater influence on predictions during the early treatment period than on longer-term efficacy estimates. Therefore, the previously proposed 8-day efficacy assessment window should not be interpreted as a definitive clinical recommendation. Prospective studies with denser sampling during the early treatment period are required to more precisely characterize the onset of BBR efficacy.

Notably, when BBR is coadministered with other non-BBR hypoglycemic agents, the onset of action can be significantly shortened, which may be related to its rich hypoglycemic effects, including increasing insulin sensitivity, promoting insulin secretion, facilitating glucose uptake, inducing glycolysis, and inhibiting glucose isomerization [43-45]. However, because there are few cross-sectional studies comparing the efficacy of BBR combined with different classes of hypoglycemic agents, it is not possible to determine whether the decrease in efficacy is due to the antagonism of BBR competing with other hypoglycemic agents or whether it is due to publication bias in the included literature.

In addition, although the theoretical maximum effect of the combined treatment was lower than that of BBR and MET, the model predicted a relatively greater reduction in FBG for the BBR & others group at higher BMI levels. Because these estimates were derived from the upper range of the simulated BMI distribution and were sensitive to the BMI-ET50 relationship, this finding should be interpreted as a model-based extrapolated trend rather than definitive evidence of superior clinical efficacy. Clinically, BBR can reduce triglyceride (TG) and serum total cholesterol (TC) levels in patients and improve related symptoms by regulating glucose-lipid metabolism [46]. In rates with high-fat diet-induced nonalcoholic fatty liver disease (NAFLD), BBR could improve symptoms by increasing total bile acid levels in the liver and faces; upregulating hepatic cytochrome 450 7A1 (CYP7A1) and microsomal triacylglycerol transfer protein (MTTP); downregulating liver X receptor α (LXRα), sterol regulatory element-binding protein (SREBP), intracellular cholesterol transporter 1, fatty acid synthase (FAS), stearoyl-CoA desaturase 1 (SCD1), fatty acid-binding protein 1 (FABP1), carnitine palmitoyl stearoyl coenzyme alpha 1, recombinant human fatty acid binding protein 1, and carnitine palmitoyltransferase 1A (CPT1A) protein levels; inhibiting fatty acid synthesis and mitochondrial complex I in the gut and liver to promote lipid metabolism and fecal lipid excretion; and ameliorating steatosis and structural lesions by inhibiting macrophage infiltration, neutrophil and hepatic stellate cell activation, proinflammatory macrophage polarization, and abnormal deposition of the extracellular matrix [47-49]. In addition, BBR also activates the AMPK/SIRT1 axis of the hepatic energy metabolism-sensing pathway in mice fed a high-fat diet and increases the expression of PPARγ-deacetylated, thermogenic proteins to promote adipose tissue remodeling, distribution, and thermogenesis [50]. Moreover, BBR also increased the abundance of Bifidobacterium bifidum and mucinophilic Ackermannia caecum contents in a genetically obese mouse model to alleviate changes such as hypertriglyceridemia and inflammation [51]. These findings generate the hypothesis that BBR-containing combination regimens may warrant further investigation in patients with higher BMI, but prospective clinical validation is required. On the basis of pharmacologic and hypoglycemic mechanisms of BBR, it is more advisable for clinicians to choose a combination therapy of BBR and MET. The two drugs exhibit strong synergistic effects in improving insulin resistance (IR) and enhancing insulin secretion. Abdominal obesity and excess visceral fat are the foundation and core of IR [52]. In addition to improving IR and lowering blood glucose, BBR+MET can also reduce the body weight and improve LDL-C, TG, and TC levels, which suggests that their IR-improving effects may be achieved through weight loss and BMI reduction [53]. Additionally, BBR+MET can stabilize the messenger RNA and upregulate LDLR expression by inhibiting proprotein convertase transcription [54]. Furthermore, chronic inflammation and oxidative stress play significant roles in diabetic retinopathy (DR), diabetic kidney disease (DKD), and diabetic neuropathy. BBR and MET also exert their hypoglycemic effects by downregulating CRP, TNF-α, and IL-6 expression levels, thereby reducing inflammatory responses [55, 56]. Based on this evidence, adding BBR-particularly in combination with MET-to existing hypoglycemic regimens

for patients with high BMIs may lead to better therapeutic outcomes.

Both the medication effect and the placebo effect were measured in this study. The outcomes showed that the placebo effect took longer than three weeks to become noticeable and was less pronounced. The simulation findings showed that the placebo response was smaller than that of any of the drug treatment groups, regardless of the patients' initial FBG levels, BMI, or duration of therapy. The results can be used to direct future analyses of placebo in the evaluation of relevant new drugs.

In the literature, in addition to BBR, some studies have used combination drugs containing BBR for treatment, such as berberine, hesperidin and chromium picolinate (BHC) and berberol. Moreover, although most of the studies included patients who received the classic diabetes drug MET in the control group, some studies included patients using other glucose-lowering drugs in the control group, such as pioglitazone and rosiglitazone. In this study, the above two treatment groups were also included in the model for analysis. After controlling for the covariate effects, the results showed that the C-BBR and N-BBR groups were inferior to the BBR group in terms of efficacy and superior to the BBR group in terms of onset of action time. The C-BBR group was comparable to the N-BBR group in terms of onset of effect time but higher than the N-BBR group in terms of efficacy, with a theoretical maximum effect value of approximately 1.9 times that of N-BBR. It should be noted, however, that due to the small amount of data included in the analysis, further data support is needed, such as group-controlled studies of different types of BBR-containing drugs and non-BBR glucose-lowering drugs.

Owing to limited reporting in the included literature, this study examined only the effects of covariates such as the publication year, daily administered dose, patient age, patient BMI, proportion of males, and baseline FBG level on the efficacy of treatment, which makes the study results somewhat limited. For example, biomarkers were not included as variables in this study since the majority of clinical trials that were included did not include biomarker categorization subgroups, and the few studies that did reported inconsistent results, which could not be categorized. This represents a significant limitation of the research. Additionally, this study revealed no correlation between age, sex, or daily dosage and clinical outcomes. Since this study solely searched the PubMed and Embase databases for literature, some articles may have been overlooked, or there may have been some publication bias.

For diabetic patients, HbA1c is the gold standard for evaluating long-term blood glucose control and treatment efficacy [57]. Elevated HbA1c levels have also been included in the diagnostic criteria for diabetes. Unfortunately, most of the clinical studies that were included in this research did not report HbA1c data, and the few studies that did could not be categorized for analysis. Therefore, this study only included FBG as the primary outcome measure. This is a limitation of the current research and also suggests that future clinical trials should be more comprehensive and long-term to lay a foundation for future quantitative analyses.

This study still has some limitations. First, this study used fasting blood glucose (FBG) as the sole efficacy endpoint to construct the E_{max} model. Although FBG is a critical and highly sensitive indicator of basal glycemic control, it does not fully reflect long-term glycated hemoglobin (HbA1c) trends, postprandial blood glucose (PBG) spikes, or daily glucose fluctuations. The selection of FBG was driven by the methodologic requirements of model-based meta-analysis (MBMA). Characterizing the non-linear time-course profile E_{max} and ET_{50} requires high-frequency, longitudinal measurements across multiple follow-up visits, which were extensively available for FBG. Conversely, HbA1c data in the included trials were sparse, making it mathematically challenging to fit a robust kinetic model. Thus, future clinical trials with dense monitoring of HbA1c, PBG, and continuous glucose monitoring parameters are needed to support a more comprehensive multi-endpoint model-based meta-analysis. Second, due to the retrospective nature of meta-analyses, some potential confounding factors, such as the duration of diabetes and patient dietary habits, were poorly or inconsistently reported across the historical trials (missing rate > 30%). Consequently, these factors could not be successfully incorporated into our covariate model,

and their effect on BBR pharmacodynamics warrants further investigation in future standardized clinical trials. Also, significant variations existed in dosing regimens, treatment durations, and baseline diabetes duration across the 28 historical trials. Although these variations were mathematically absorbed through between-study variability (ω) and residual weighting in our nonlinear mixed-effects model, hierarchical subgroup modeling based on exact diabetes duration or dose-tiering was restricted by data sparsity in specific subgroups. Consequently, the model outputs serve as population-level quantitative projections rather than definitive clinical dosing conversion protocols. Third, our systematic literature search was restricted to PubMed and Embase databases, and only English-language articles were included. This restrictive strategy may lead to literature omission and potential publication bias. Fourth, a substantial variation was observed in study sample sizes (ranging from 9 to 100 subjects per arm) and dosing schedules across the historical trials. While the non-linear Emax model adjusted for sample-size weighting, this high baseline heterogeneity may limit the mathematical model's extrapolation and generalization performance when applied to larger, strictly standardized target clinical populations. Fifth, in this MBMA framework, study heterogeneity is formally addressed through covariate adjustment and estimation of between-study variability (ω), rather than using traditional statistical measures of heterogeneity. Due to the limited number of clinical trials within certain drug subgroups, no formal tests for publication bias (such as the Egger test) or sensitivity analyses using exclusion methods were conducted. Nevertheless, robust bootstrap results (a 91% success rate) confirm the overall stability of the parameters; however, these statistical limitations must still be considered when extrapolating model results.

Conclusion

For the first time, the glucose-lowering effects and temporal characteristics of BBR, MET, placebo, and other hypoglycemic medicines were measured and compared, along with their effectiveness in patients with varying BMIs, treatment cycles, and baseline FBG levels. Within the simulated BMI range of 18-36 kg/m^2, the predicted glucose-lowering efficacy of all treatment groups decreased as BMI increased, and the between-treatment differences became markedly smaller at the upper end of the simulated range. Therefore, considering its lower side effects, BBR may represent a treatment option for such patients, although this finding requires prospective clinical validation. When combined with non-BBR hypoglycemic medications, BBR also had a significantly shorter time to the beginning of the effect than the other medicines. However, the relatively high uncertainty surrounding ET_{50} limits precise determination of the early treatment-onset window, and the timing of efficacy assessment should therefore be interpreted cautiously. In the future, we will conduct more extensive research on long-term blood glucose control based on HbA1c levels, as well as subgroup analyses on medication dosage and combination therapies. This study provides quantita tive data required for future clinical studies and diabetes-related guidelines.

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Disclosure of conflict of interest

None.

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Table S1. Search strategy

No.	Query	Results	Dates
PubMed			
#1	("Berberine" [56] OR "Berberol" OR "BBR" OR "Berberina") AND ("Glycated Hemoglobin A" [56] OR "Glucose" [56] OR "Fasting blood glucose" OR "FBG" OR "Postprandial glucose" OR "PPG")	260	30-Jun-2022
EMBASE			
#1	("berberine"/exp OR berberol OR bbr OR berberina) AND ("glucose"/exp OR "hemoglobin a1c"/exp OR "fasting blood glucose"/exp OR "postprandial blood glucose"/exp OR fbg OR ppg)	768	30-Jun-2022

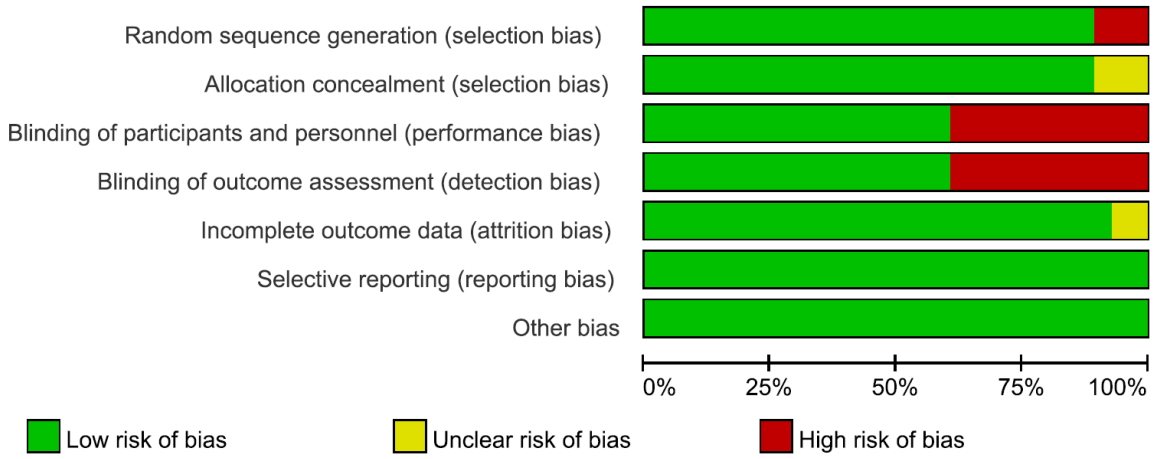


Figure S1. Summary results of the literature quality assessment.

Berberine for lowering blood glucose

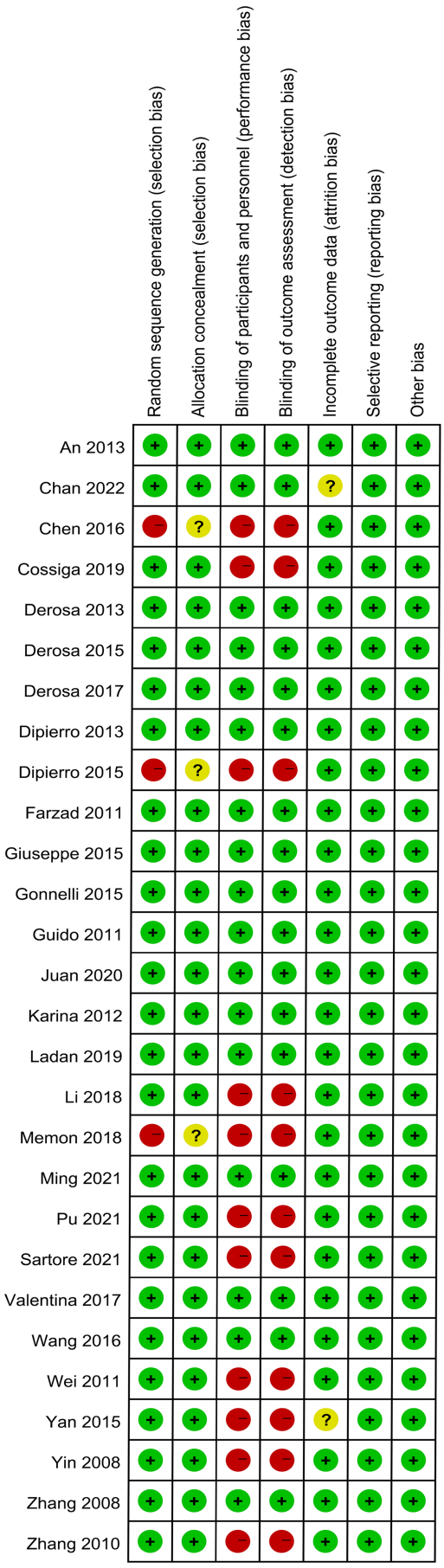


Figure S2. Detailed literature quality assessment.

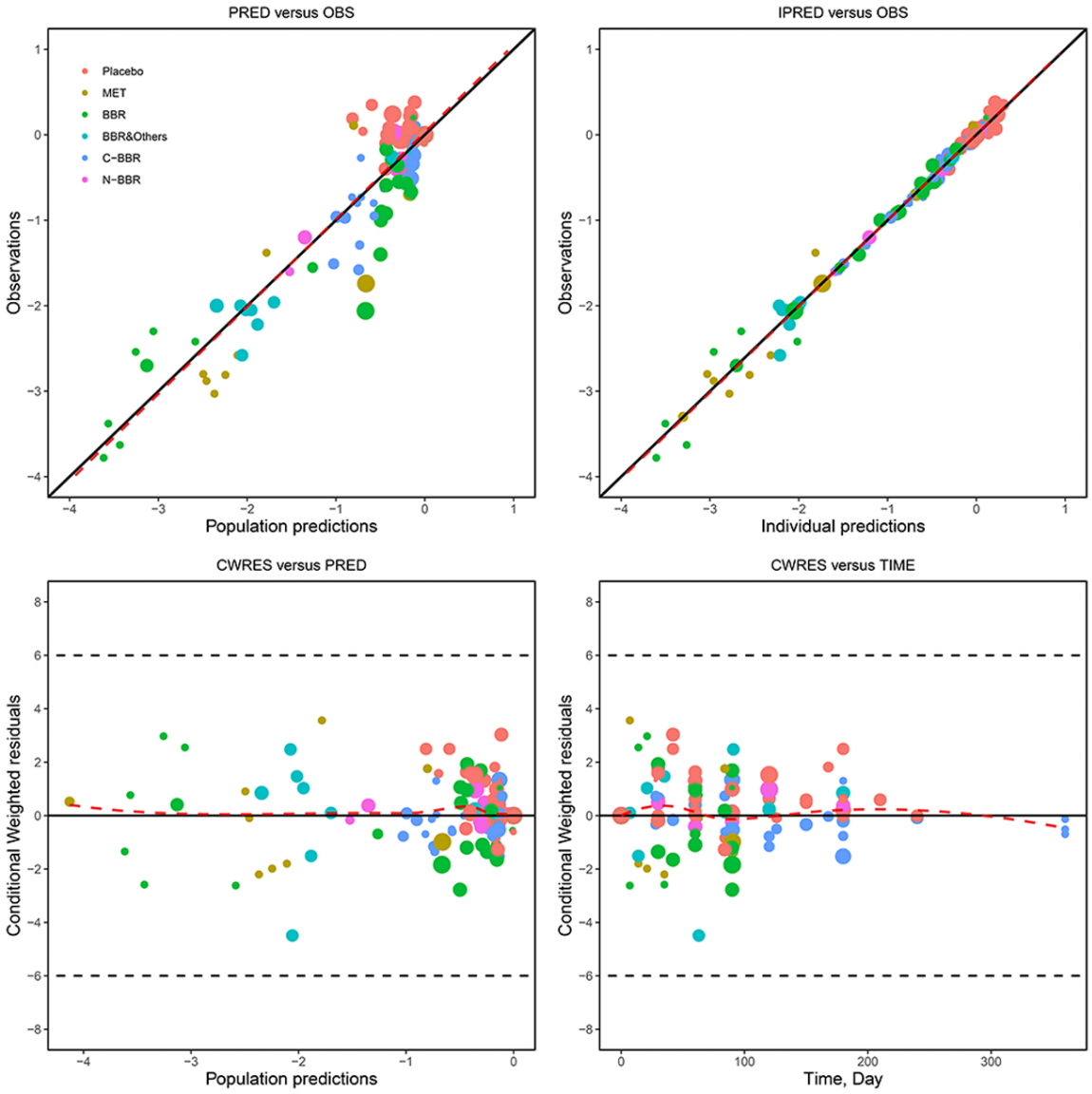


Figure S3. Final goodness-of -fit graph of the models.

Table S2. Scenario sensitivity analysis of the influence of ET_{50} uncertainty on the predicted proportion of Emax achieved over time

Time	ET_{50} = 0.10 days	ET_{50} = 3.13 days	ET_{50} = 21.76 days
Day 5	98.0%	61.5%	18.7%
Day 8	98.8%	71.9%	26.9%
Day 10	99.0%	76.2%	31.5%
Day 30	99.7%	90.6%	58.0%
Day 90	99.9%	96.6%	80.5%

Notes: Values represent the predicted percentage of theoretical maximum efficacy (Emax) achieved at each time point according to $E(t)/E_{max} = t/(ET_{50}+t)$. The three ET_{50} scenarios correspond to the lower limit of the bootstrap 95% CI (0.10 days), the final model point estimate (3.13 days), and the upper limit of the bootstrap 95% CI (21.76 days), respectively. Other model parameters were held constant.

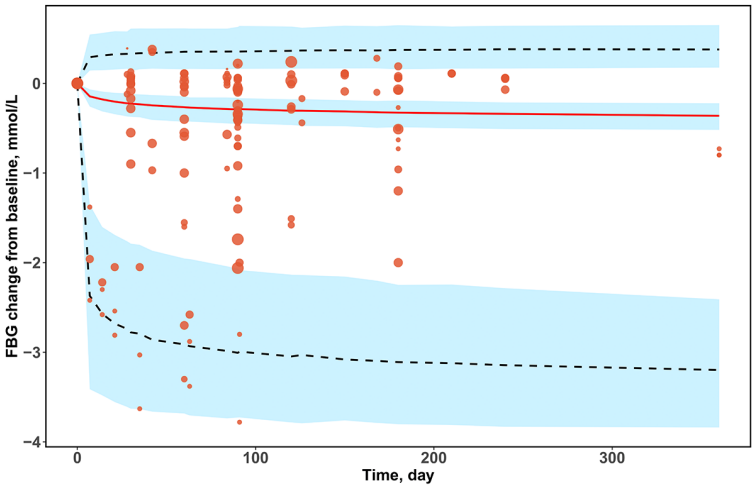


Figure S4. Final visual predictive view of the models.