International Journal of Basic & Clinical Pharmacology
Chaudhary PS et al. Int J Basic Clin Pharmacol. 2025 Sep;14(5):694-699
http://www.ijbcp.com
pISSN 2319-2003 | eISSN 2279-0780

DOI: https://dx.doi.org/10.18203/2319-2003.ijbcp20252563

Original Research Article

Comparative study of efficacy and safety of berberine hydrochloride versus metformin in newly diagnosed prediabetic patients: a randomized clinical trial

Prashant S. Chaudhary[1]*, Shweta V. Deshmukh[2], Deepali Jaybhaye[3], Sukhmeen Kaur[3]

[1]Department of Pharmacology, Parbhani Medical College, Parbhani, Maharashtra, India
[2]Department of Community Medicine, Govt medical College, Chh. Sambhajinagar, Maharashtra, India
[3]Department of Pharmacology, Shree Ramchandra Institute of Medical Sciences, Ch. Sambhajinagar, Maharashtra, India

Received: 05 August 2025
Revised: 18 August 2025
Accepted: 20 August 2025

***Correspondence:**
Dr. Prashant S. Chaudhary,
Email: drprashantmgm@gmail.com

ABSTRACT

Background: Prediabetes is a growing public health concern in India, with high rates of progression to type 2 diabetes and associated complications. Metformin is widely recommended but has gastrointestinal side effects that may limit adherence. Berberine hydrochloride, a plant-derived alkaloid with antidiabetic properties, has shown promise as an alternative therapy. A randomized, open-label, parallel-group clinical trial was conducted in newly diagnosed prediabetic adults.
Methods: Ninety participants were randomly allocated to receive Berberine HCl 500 mg twice daily or Metformin 500 mg twice daily for 12 weeks. Primary outcomes included change in fasting plasma glucose (FPG), postprandial plasma glucose (PPG), and HbA1c. Secondary outcomes included adverse events.
Results: Berberine HCl reduced mean FPG from 109.8±4.6 mg/dl to 97.2±3.6 mg/dl (−12.6±2.4 mg/dl) and PPG from 156.4±6.8 mg/dl to 134.6±5.4 mg/dl (−21.8±3.9 mg/dl). Metformin reduced FPG from 110.2±4.8 mg/dl to 99.4±3.8 mg/dl (−10.8±2.5 mg/dl) and PPG from 157.1±7.0 mg/dl to 137.8±5.6 mg/dl (−19.3±4.0 mg/dl). HbA1c decreased by 0.31% in the Berberine group and 0.28% in the Metformin group, with a significant between-group difference at week 12 (p=0.04). Gastrointestinal upset occurred in 20% of Berberine recipients compared to 30% in the Metformin group.
Conclusions: Berberine HCl demonstrated glycemic efficacy comparable to Metformin in prediabetic patients, with fewer gastrointestinal adverse events, suggesting its potential as an alternative therapy for individual's intolerant to Metformin.

Keywords: Prediabetes, Berberine hydrochloride, Metformin, Glycemic control, Clinical trial, India

INTRODUCTION

Prediabetes with impaired fasting glucose or impaired glucose tolerance is a critical state for early interventions to prevent the progression to type 2 diabetes mellitus (T2DM) and its accompanying complications. Prevalence of prediabetes is high worldwide, with India reporting wide variation from ~10% in some studies to > 30% in others.[1,2] Those with prediabetes are at heightened risk of developing microvascular and macrovascular complications, cardiovascular disease (CVD), stroke, and mortality even before frank diabetes ensues .[3] Metformin is still the pharmacotherapy-of-choice for postponing diabetes among high-risk individuals. Metformin has demonstrated treatment efficacy in preventing progression to T2DM, and is generally more effective in younger or obese populations, although invalidation occurs due to the numerous of side effects like dyspepsia and variable

patient adherence.[4] Berberine is an important plant alkaloid having various biological activities, while berberine hydrochloride (HCl) has been recognized as one of the new candidates. It exerts its effects on glycemia by activating hepatic AMP-activated protein kinase (AMPK), increasing insulin sensitivity, altering lipid metabolism, and modulation of gut microbiome, which have shown some promising results in a few small trials among prediabetic and diabetic subjects.[5] Despite this potential, there exists a paucity of direct comparative data between berberine HCl and metformin in the Indian prediabetic population, where genetic, environmental, and dietary factors might influence therapeutic response. Hence, this study aims to assess and compare the efficacy and safety of berberine HCl versus metformin in newly diagnosed prediabetic patients.

METHODS

A prospective, randomized, open-label, parallel-group clinical trial was carried out in a tertiary care hospital MGM Medial College & Hospital Aurangabad Maharashtra, to assess the efficacy and safety of berberine hydrochloride compared with metformin in newly diagnosed prediabetes patients during period of September 2014 to October 2025.

Inclusion criteria for this study were adults newly diagnosed with prediabetes according to the American Diabetes Association (ADA) criteria, defined as having impaired fasting glucose between 100–125 mg/dl, 2-hour postprandial glucose between 140–199 mg/dl, and/or HbA1c between 5.7–6.4%. Individuals willing to provide informed consent and comply with study visits and procedures were included. Exclusion criteria included patients with previously diagnosed type 2 diabetes mellitus, those already receiving antidiabetic medications, or individuals with significant hepatic, renal, or cardiovascular disease were excluded.

Additional exclusion criteria included pregnancy or lactation, known allergy or intolerance to either berberine hydrochloride or metformin, active gastrointestinal disorders that could interfere with drug absorption or tolerance, and any other medical condition deemed unsuitable by the investigators. Eligible patients who met the inclusion criteria and signed the informed consent form were randomly divided into two groups at a ratio of 1:1: Group A was treated with berberine HCl, and Group B with metformin. Randomization was performed using a computer-generated sequence with sealed opaque envelopes to ensure allocation concealment. Each participant underwent the study for 12 weeks and had follow-up visits before start of treatment (baseline), at 4, 8, and 12 weeks. Patients were reviewed and evaluated using a standard proforma at each visit including clinical evaluation, anthropometric measurements (weight obtained to the nearest 0.1 kg, while standing without shoes; height was measured to the nearest 0.5 cm), blood investigations (fasting plasma glucose-FPG and post prandial plasma glucose-PPG levels) and haemoglobin A1c (Hb-A1C) %. Assessment of Drug Safety. Liver and renal function tests were performed (at baseline) and at the end of the study. At each visit, adverse events were recorded and compliance was assessed by pill count. The primary outcome was the mean change in fasting plasma glucose and HbA1c from baseline to 12 weeks for between the two groups. The presence of postprandial plasma glucose, weight changes and body mass index (BMI) was evaluated as the secondary outcomes. Statistical tests for data analysis, as applicable were used and a significant difference was determined by $p<0.05$ This study was approved by the Institutional Ethics Committee, and all procedures described were in accordance with the good clinical practice and the declaration of Helsinki.

RESULTS

The results of this randomized controlled trial are presented in the following section (Figure 1), beginning with the baseline demographic and clinical characteristics of participants in the Berberine HCl and Metformin groups. This is followed by comparative analyses of changes in fasting plasma glucose (FPG), postprandial plasma glucose (PPG), and HbA1c over the 12-week study period. The safety profile, including the incidence and types of adverse events, is also detailed to assess tolerability of both interventions.

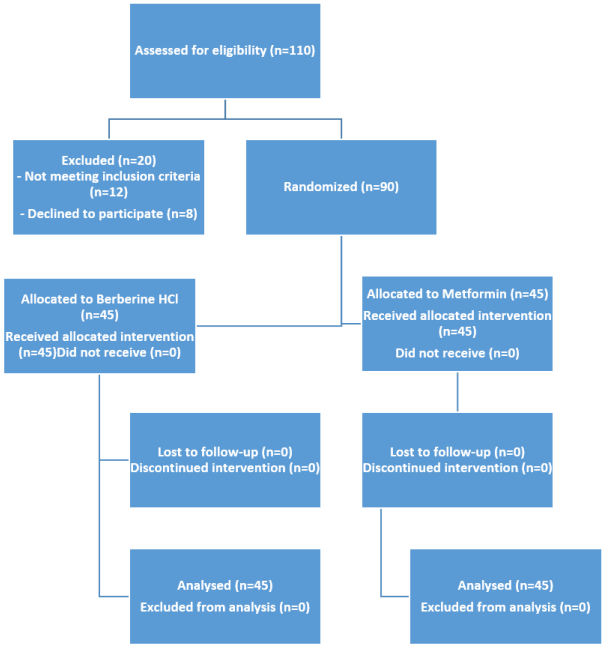


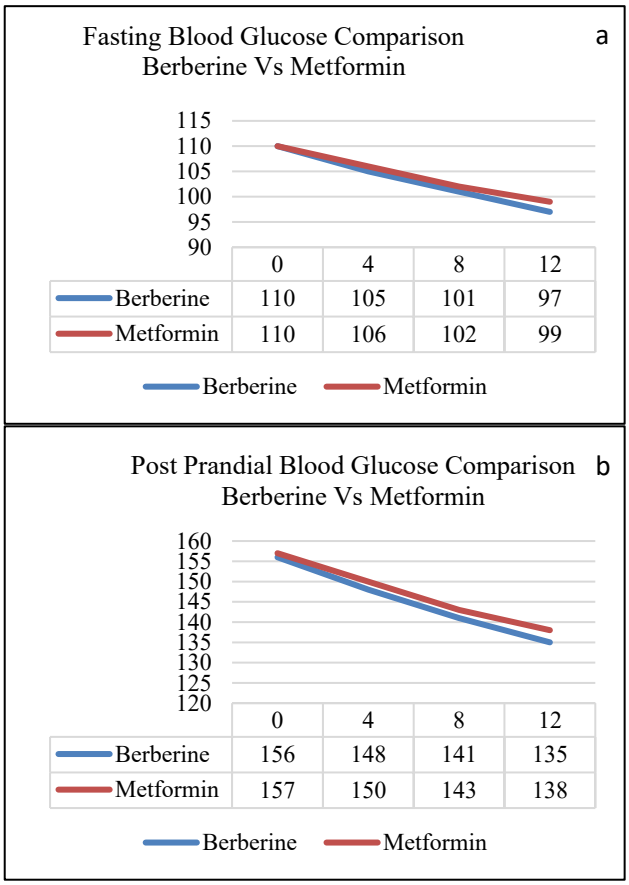
Figure 1: Consort flow diagram depicting participant enrollment, allocation, follow-up, and analysis in the comparative study of berberine Hcl and metformin in prediabetes (n=45 per group)".

Table 1 shows that there were no significant differences in the numbers of subjects who received either Berberine HCl or metformin in relation to any baseline demographic and clinical factor (Table 1). The average age of the study

subjects was 44.3±8.1 years in the Berberine group, and 45.1±7.9 years in the Metformin group (p value=0.65). The proportion of male participants was not significantly different between Berberine and Metformin groups (60.0% vs. 62.2%, p=0.83). The mean BMI was similar (27.4 ±2.8 vs 27.1±2.6 kg/m², p=0.58). By considering baseline values for fasting plasma glucose (111.2±6.9 vs. 112.4±7.1 mg/dl; p=0.39), postprandial plasma glucose (158.6±12.4 vs. 160.1±tablc and HbA1c (6,12±d^ / og^j%; p=oVz) feminist! There were 26.7% and 28.9% subjects showing comorbidities in Berberine group and Metformin group, respectively (p=0.81), confirming that randomization achieved comparable baseline profiles. Table 2 shows that there was no significant difference in basic laboratory parameters between Berberine HCl and Metformin (Table 2). Patient in the Berberine group had mean ALT levels of 28.6±6.1 IU/l and AST levels of 27.4±5.8 IU/l compared to those in the Metformin group with mean ALT levels of 29.1±6.4 IU/l (p=0.71) and AST levels of 28.0±6.0 IU/l (p=0.65). Average bilirubin levels were higher in the Berberine group compared with mean levels on Metformin (0.78±0.12 mg/dl vs 0.80±0.14 mg/dl p=0.52). Values of serum creatinine were also similar in the two groups (0.84±0.09 mg/dl vs. 0.85±0.10 mg/dl, p=0.77). Total cholesterol (192.4±18.6 mg/dl vs. 190.8±17.9 mg/dl; p=0.68), LDL-C (116.2±14.5 mg/dl vs. 115.8±13.9 mg/dl; p=0.89), HDL-C (42.6±5.8 mg/l vs 43.1±6.0 mg/l, p=0·71) and triglycerides (152.8±18.1 mg/l vs 150.9±17.4 mg/l, p=0.59) were similarly distributed at baseline, indicating that the two study groups had well matched biochemical profiles prior to randomisation.

Table 3 shows that, during the 12-week study period, fasting plasma glucose (FPG) decreased significantly from baseline in both groups of patients. In Berberine group the mean FPG was decreased from 109.8±4.6 to 97.2±3.0 mg/ at week 12, and the mean change was −12.6±2.4 mg/dl. The FPG in the Metformin group was reduced from a mean of 110.2±4.8 mg/dl to 99.4±3.8 mg/dl, yielding a mean reduction of −10.8±2.5 mg/dl (Table 2). The mean change in FPG differed between groups (p=0.01), showing that groups treated with Berberine experienced slightly greater decreases in FPG at week 12. Between-group differences reached statistical significance only at week 12.

Table 4 shows that patients in both groups had significant reductions in postprandial plasma glucose (PPG), though. After 12 weeks of Berberine HCl treatment, according to the repeated-measures ANOVA, significant improvement in the mean PPG level was observed (p<0.01) Metformin group ↓ from 157.1±7.0 mg/dl to 137.8±5.6 mg/dl, mean change −19.3±4.0 mg/dl end result. The between group differences at weeks 4 and 8 was not statistically significant but by week 12 Berberine appeared to improve more (p=0.01) There was also a higher response rate in the Berberine group with respect to haemoglobin and ferritin versus placebo (p=0.05). Overall mean change from baseline favoured Berberine as well (p=0.03). According to Table 5, the mean patient HbA1c values at baseline was not significantly different between Berberine HCl group (6.18±0.22%) and Metformin group (6.21±0.20%, p=0.48). HbA1c levels had significantly decreased within both groups after 12 weeks; falling to 5.87 ± 0.20% in the Berberine group (p There was also a statistically significant difference at week 12 between groups (p=0.04) where Berberine continued to slightly improve. Nevertheless, the change from baseline in mean (95% CI) did not differ significantly between both groups (−0.31 (−0.08, −0.53) % for Berberine versus −0.28 (−0.09, −0.46) (p=012).



Figures 2: (a, b) Trends in glycemic parameters over 12 Weeks for Berberine HCl and Metformin.

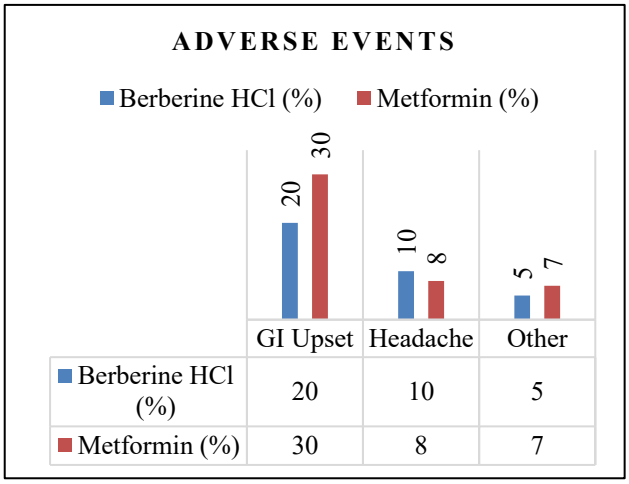


Figure 3: Adverse event profile comparison.

Figure 2 shows that fasting plasma glucose (FPG), postprandial plasma glucose (PPG), and HbA1c decreased progressively in both the Berberine HCl group and the metformin group after 12 weeks of treatment. In the Berberine HCl group, FPG fell from 110 mg/dl to 97 mg/dl, PPG from 156 to only 135 mg/dl, and HbA1c from 6.18% to 5.87%. In the Metformin group also FPG reduced from 110 mg/dl to 99 mg/dl, PPG from 157mg/dl to 138 mg/dl and HbA1c from 6.21% to5.93%. Both treatments were effective overall, and the glycemic parameters improved with Berberine HCl, showing a mud improvement by week 12. According to Figure 3, the most frequent side effect in both groups was gastrointestinal (GI) upset being reported by 20% and 30% of participants in the Berberine HCl and Metformin group, respectively. There was 10 % of headaches reported by the participants in the Berberine HCl group and 8% in Metformin group. The most common adverse events were gastrointestinal and flatulence (5% of Berberine HCl participants, 7% for Metformin).

Table 1: Baseline demographic and clinical characteristics of participants.

Variable	Berberine HCl group (n=45)	Metformin group (n=45)	P value
Age (years), mean±SD	44.3±8.1	45.1±7.9	0.65
Male (%)	27 (60.0%)	28 (62.2%)	0.83
BMI (kg/m^2), mean±SD	27.4±2.8	27.1±2.6	0.58
FPG (mg/dl), mean±SD	111.2±6.9	112.4±7.1	0.39
PPG (mg/dl), mean±SD	158.6±12.4	160.1±11.7	0.54
HbA1c (%), mean±SD	6.12±0.25	6.15±0.28	0.72
Comorbidities (%)	12 (26.7%)	13 (28.9%)	0.81

Table 2: Baseline laboratory parameters.

Parameter	Berberine HCl group (n=45)	Metformin group (n=45)	P value
ALT (IU/l), mean±SD	28.6±6.1	29.1±6.4	0.71
AST (IU/l), mean±SD	27.4±5.8	28.0±6.0	0.65
Bilirubin (mg/dl), mean±SD	0.78±0.12	0.80±0.14	0.52
Serum creatinine (mg/dl), mean±SD	0.84±0.09	0.85±0.10	0.77
Total cholesterol (mg/dl), mean±SD	192.4±18.6	190.8±17.9	0.68
LDL-C (mg/dl), mean±SD	116.2±14.5	115.8±13.9	0.89
HDL-C (mg/dl), mean±SD	42.6±5.8	43.1±6.0	0.71
Triglycerides (mg/dl), mean±SD	152.8±18.1	150.9±17.4	0.59

Table 3: Change in fasting plasma glucose (mg/dl) over 12 weeks.

Time point	Berberine HCl (mean±SD)	Metformin (mean±SD)	P value
Baseline	109.8±4.6	110.2±4.8	0.68
Week 4	104.6±4.2	105.8±4.4	0.19
Week 8	100.8±3.9	102.4±4.1	0.07
Week 12	97.2±3.6	99.4±3.8	0.02*
Mean change from baseline	−12.6±2.4	−10.8±2.5	0.01*

Note:*- p<0.05 considered statistically significant.

Table 4: Change in postprandial plasma glucose (mg/dl) over 12 weeks.

Time point	Berberine HCl (mean±SD)	Metformin (mean±SD)	P value
Baseline	156.4±6.8	157.1±7.0	0.74
Week 4	148.2±6.2	150.0±6.5	0.21
Week 8	141.0±5.8	143.4±6.0	0.09
Week 12	134.6±5.4	137.8±5.6	0.01*
Mean change from baseline	−21.8±3.9	−19.3±4.0	0.03*

Note:*- p<0.05 considered statistically significant.

Table 5: Change in HbA1c (%) over study period.

Time point	Berberine HCl (mean±SD)	Metformin (mean±SD)	P value
Baseline	6.18±0.22	6.21±0.20	0.48
Week 12	5.87±0.20	5.93±0.19	0.04*
Mean change from baseline	−0.31±0.08	−0.28±0.09	0.12

Note:*- p<0.05 considered statistically significant.

In summary, although both were largely well-tolerated, there was a higher incidence of Gastrointestinal GI upset in the Metformin group compared to the Berberine HCl group.

DISCUSSION

The present study compared the efficacy and safety of Berberine HCl as well as with Metformin on lifestyle modification in newly diagnosed prediabetic individuals over a 12-week period. Both groups had significant alterations in glycaemic parameters, but the lowering of FPG and PPG levels was more marked with Berberine HCl than Metformin. These findings are consistent with earlier studies showing Berberine could lower blood glucose similarly to Metformin by simultaneously targeting multiple pathways, such as activating AMP-activated protein kinase (AMPK), enhancing insulin receptor expression, and regulating gut microbiota.[6,7]

Both groups presented a significant reduction in HbA1c from baseline up to week 12, with no statistically significant difference between them. While this does indicate that Berberine has some insufficient edge over Metformin in the short-term glycemic control, despite a similar long-term glycemic impact on prediabetics of Metformin in comparison to Berberine as suggested by previous trials and meta-analyses.[8]

Gastrointestinal (GI) upset was more common in the Metformin group (30%) compared with the Berberine HCL group (20%). This is in agreement with the potent GI side effects of Metformin, mediated by its direct action on the gut mucosa and alteration in bile salt metabolism.[1,9] Berberine was well tolerated in general but with a slightly increased frequency of headache and mild GI upset, which has also been reported in other safety evaluations of herbal medicines.[10]

These findings are particularly relevant from the clinical point of view, in a background of rising epidemic of prediabetes in India with rapid progression to type 2 diabetes if not attended timely.[11] This perhaps makes Berberine HCl an exciting alternative or indeed additive to Metformin in healthy individuals intolerant to the latter given its equivalent efficacy and superior GI adverse event profile. Nevertheless, larger and longer trials are needed to substantiate its long-term safety and diabetic preventive effect.

This study was limited by its relatively short duration of 12 weeks, which may not fully capture the long-term efficacy and safety of berberine hydrochloride compared with metformin in prediabetic patients. The open-label design could introduce bias in reporting of adverse events, and the modest sample size from a single tertiary care center may restrict the generalizability of findings.

CONCLUSION

In this 12-week comparative study, both Berberine HCl and Metformin significantly improved glycemic parameters in newly diagnosed prediabetic individuals. Berberine HCl reduced fasting plasma glucose from 109.8±4.6 mg/dl to 97.2±3.6 mg/dl (−12.6±2.4 mg/dl) and postprandial plasma glucose from 156.4±6.8 mg/dl to 134.6±5.4 mg/dl (−21.8±3.9 mg/dl), while Metformin achieved reductions from 110.2±4.8 mg/dl to 99.4±3.8 mg/dl (−10.8±2.5 mg/dl) and from 157.1±7.0 mg/dl to 137.8±5.6 mg/dl (−19.3±4.0 mg/dl), respectively. HbA1c decreased by 0.31% in the Berberine HCl group and 0.28% in the Metformin group, with a significant between-group difference at week 12 (p=0.04).

Gastrointestinal upset occurred in 20% of Berberine users compared to 30% with Metformin, indicating a better tolerability profile. These findings suggest that Berberine HCl is at least as effective as Metformin for short-term glycemic control in prediabetes, with fewer gastrointestinal adverse events, and could be considered as an alternative in individuals intolerant to Metformin.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Anjana RM, Deepa M, Pradeepa R, et al. Prevalence of diabetes and prediabetes in 15 states of India: the ICMR–INDIAB study. Lancet Diabetes Endocrinol. 2017;5(8):585–96.
2. Mohan V. Global prevalence of prediabetes and diabetes in urban and rural India. Diabetes Care. 2023;46(12):220.
3. Schlesinger S, Aleksandrova K, Pischon T. Prediabetes and risk of mortality and diabetes-related complications: umbrella review. Ann Med. 2021;53(1):1400–12.
4. Patel D. The effectiveness of metformin in diabetes prevention. Indian J Endocrinol Metab. 2023;11:985.
5. Panigrahi A, et al. Efficacy and safety of HIMABERB® (berberine HCl) on glycemic markers in prediabetes. J Ethnopharmacol. 2023;8:728.
6. Yin J, Xing H, Ye J. Efficacy of berberine in patients with type 2 diabetes mellitus. Metabolism. 2008;57(5):712–7.
7. Turner N, Li JY, Gosby A. Berberine and its derivatives: a novel class of AMPK activators with potential metabolic and anti-obesity effects. Diabetes. 2008;57(5):1414–8.
8. Dong H, Wang N, Zhao L, Lu F. Berberine in the treatment of type 2 diabetes mellitus: a systematic review and meta-analysis. Evid Based Complement Alternat Med. 2012;2:591654.

9. McCreight LJ, Bailey CJ, Pearson ER. Metformin and the gastrointestinal tract. Diabetologia. 2016;59(3):426–35.
10. Imenshahidi M, Hosseinzadeh H. Berberis vulgaris and berberine: an update review. Phytother Res. 2016;30(11):1745–64.
11. Anjana RM, Deepa M, Pradeepa R. Prevalence of diabetes and prediabetes in 15 states of India: results from the ICMR-INDIAB population-based cross-sectional study. Lancet Diabetes Endocrinol. 2017;5(8):585–96.

Cite this article as: Chaudhary PS, Deshmukh SV, Jaybhaye D, Kaur S. Comparative study of efficacy and safety of berberine hydrochloride versus metformin in newly diagnosed prediabetic patients: a randomized clinical trial. Int J Basic Clin Pharmacol 2025;14:694-9.