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Antidiabetic Potential of *Piper crocatum*: A Systematic Review of In Silico, In Vitro, In Vivo, and Clinical Evidence

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ABSTRACT

Introduction*: Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia, affecting 463 million individuals worldwide in 2019. If inadequately controlled, DM leads to progressive and serious complications. Current management relies on oral antidiabetic agents and insulin therapy, but both are associated with adverse effects, driving interest in medicinal plants as complementary or alternative therapies. Piper crocatum (red betel), a tropical species widely cultivated in Indonesia, has long been used in traditional medicine and is increasingly recognized for its antidiabetic potential.* ***Aims****: This review critically synthesizes available evidence on the pharmacological effects of Piper crocatum in diabetes management.* ***Method****: Literature was systematically retrieved from Google Scholar using keywords "(Piper crocatum) AND ((Antidiabetic) OR (Antihyperglycemic))", screened through Covidence software, and evaluated according to PRISMA guidelines.* ***Result****: From an initial 500 records, 25 studies met the inclusion criteria. Findings from in silico, in vitro, in vivo, and clinical trials consistently support the glucose-lowering activity of Piper crocatum, highlighting it as a promising natural antidiabetic candidate.* ***Conclusion****: Future research should prioritize formulation development to enable downstream translation of Piper crocatum into Obat Herbal Terstandar (OHT) and Fitofarmaka*

KEYWORDS*: Piper crocatum, red betle, antidiabetic, antihyperglicemic, in silico, in vitro, in vivo, clinical trials.*

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disease defined by persistent hyperglycemia. Excess circulating glucose undergoes non-enzymatic interactions with plasma proteins, resulting in the production of glycated derivatives such as hemoglobin and albumin. The progressive accumulation of these advanced glycation end products plays a central role in the onset and progression of diabetes-related complications (Nor et al. 2023). On a global scale, the prevalence of diabetes was estimated at 588.7 million cases in 2019 and is anticipated to escalate by 45% to 852.5 million by 2050 (Duncan, Magliano &

Boyko 2025). In Indonesia, the burden is equally alarming, with 18.69 million cases documented in 2020 and projections suggesting a doubling to 40.7 million cases by 2045 (Wahidin et al. 2024).

If left unmanaged, diabetes mellitus progressively predisposes patients to a wide range of chronic complications such as macrovascular disease, retinopathy, nephropathy, neuropathy, diabetic foot syndrome, heightened vulnerability to infections, muscle disorders, osteoporosis, joint pathologies, and hepatic impairment (Meilani et al. 2024). Conventional treatment relies largely on oral antidiabetic agents and insulin therapy; however, these interventions are frequently limited by adverse effects. Reported complications of pharmacological treatment include hypoglycemia, gastrointestinal discomfort, headaches, generalized weakness, fatigue, chest pain, and throat irritation, among others. Considering these limitations, interest in medicinal plants as complementary or alternative therapeutic options has increased substantially. The use of botanicals with antidiabetic properties is deeply rooted in traditional medicine, with evidence of practice spanning thousands of years and persisting in contemporary healthcare systems (Cherrada et al. 2024; Prajapati et al. 2024).

Piper crocatum, popularly referred to as red betel, is a tropical species extensively grown in Indonesia (Maslikah & Putra 2024). Although currently widespread in Southeast Asia, this medicinal shrub is believed to have originated from Peru (Safithri, Bintang & Syaefudin 2023). Traditionally, *P. crocatum* has been valued for its therapeutic applications against a wide range of diseases. Its pronounced antibacterial and anti-inflammatory activities underpin its empirical use in treating oral and dental infections (Maslikah et al. 2025), potential in regulating hyperglycemia (Damanik, Manafe & Kareri 2024), exerting antihypertensive activity (Panjaitan et al., 2024), and reducing uric acid related disorders such as gout (Wahyuningsih et al. 2022).

P. crocatum is rich in secondary metabolites, comprising alkaloids, flavonoids, phenolic compounds, steroidal glycosides, saponins, tannins, quinones, essential oils, chalcones, anthocyanins, triterpenoids, and steroids (Damanik, Manafe & Kareri 2024; Irawan et al. 2024; Kurnia et al. 2024). A wide range of pharmacological properties have been documented, including antioxidant potential (Astyka et al. 2024; Irawan et al. 2024; Nursamsiar, Marwati & Nur 2023), inhibition of acetylcholinesterase (Nurinsani, Andrianto & Safithri 2024), and suppression of key carbohydrate-digesting enzymes such as α-glucosidase (Hartini &

Setyaningsih 2023; Irawan et al. 2024) and α-amylase (Hartini & Setyaningsih 2023). Additional reported activities encompass antimelanogenesis (Safithri et al. 2023), nephroprotection (Dewi et al. 2023), antibacterial efficacy against *Staphylococcus aureus* (Astyka et al. 2024) and other oral pathogens (Kurnia et al. 2024), acceleration of wound healing (Suswidiantoro et al. 2025), and protection of ocular tissues under diabetic conditions (Damanik, Manafe & Kareri 2024). Furthermore, *P. crocatum* exhibits cytotoxic effects against MCF-7 breast cancer cells (Nursyarah, Safithri & Andrianto 2023), demonstrates both antidiabetic and anti-atherosclerotic actions in diabetes (Adiansyah et al. 2023), reduces the production of inflammatory mediators such as TNF-α and ICAM-1 (Lely et al. 2023), and provides analgesic (Hermanto, Suherman & Rahmawati 2022), hepatoprotective (Lister et al. 2022), and antihyperuricemic benefits (Wahyuningsih et al. 2022).

A growing body of evidence highlights the antidiabetic potential of *P. crocatum*, particularly in its ability to modulate hyperglycemia. Several previous review studies have investigated the potential of *P. crocatum*, including its activity against oral microorganisms (Kurnia et al. 2024), its phytochemical profile and antibacterial effect against dental caries bacteria (Heliawati et al. 2022), antifungal activity (Siswina et al. 2022), traditional uses and pharmacological properties (Azzahra et al. 2025), as well as the effect of its decoction on reducing blood glucose levels (Saputri & Riamah 2025). However, to date, no reports have addressed the antidiabetic potential of *P. crocatum* based on *in* silico, *in vitro*, *in vivo*, and clinical trial approaches. Based on background, this review aims to critically synthesize existing findings regarding the pharmacological effects of *P. crocatum* in diabetes management. By integrating available data, the review concludes to delineate the current state of research on this species and to identify knowledge gaps that may guide future scientific exploration.

METHODS

Research Strategy

Literature searches were carried out through Google Scholar using the Publish or Perish (PoP) application to identify studies addressing the antidiabetic activity of *Piper crocatum*. The query applied was "(Piper crocatum) AND ((Antidiabetic) OR (Antihyperglycemic))," executed on July 5, 2025. Bibliographic metadata were extracted for articles published between January 1, 2020 and July 5, 2025, with the search output capped at a maximum of 500 records.

Eligibility Criteria

Inclusion criteria were defined as follows: (1) original research articles publi-

shed in either English or Indonesian; (2) studies that specifically utilized *Piper crocatum* as the research sample; (3) investigations that examined its antidiabetic or antihyperglycemic activity; and (4) research conducted through *in silico*, *in vitro*, *in vivo*, or clinical trials. Exclusion criteria included: (1) review papers; (2) book chapters; (3) studies that were not accessible in full text; (4) publications not meeting the stated inclusion requirements; and (5) studies that were not contain antidiabetic or antihyperglycemic research, especially through *in silico*, *in vitro*, *in vivo*, or clinical approach.

Literature Screening and Data Extraction

Following the retrieval of metadata from Google Scholar through the Publish or Perish (PoP) application, screening and data extraction were performed using Covidence (www.covidence.org) in accordance with the PRISMA guidelines. After the software automatically removed duplicate records, a total of 496 articles were identified from 500 articles. Title and abstract screening was independently conducted by two reviewers based on predefined inclusion and exclusion criteria. Articles deemed irrelevant were excluded, and the full texts of potentially eligible studies were subsequently assessed to confirm eligibility and extract the required data. The selection process is illustrated in the PRISMA flow diagram (Figure 1 and 2).

RESULTS AND DISCUSSION

Study Selection

From the initial search, 500 records were identified in Google Scholar. Following the removal of duplicates, 496 unique studies underwent eligibility screening, yielding 25 articles that satisfied the inclusion criteria for this review. The selected publications, dated between January 1, 2020 and July 5, 2025, were most frequently published in 2023 (n = 8), followed by 2024 (n = 6) (Fig. 2A). Collectively, these 25 studies explored the antidiabetic activity of *P. crocatum* using diverse methodologies, encompassing *in silico* modeling, *in vitro* assays, *in vivo* experiments, and clinical evaluations. Specifically, one study utilized an *in silico* design, eight employed *in vitro* techniques, thirteen involved *in vivo* models, and three represented clinical trials (Fig. 2B).

In Silico Study

In silico studies represent computational strategies employed to discover and design novel drug candidates by integrating molecular modeling tools with computer-aided drug design (CADD) approaches, including virtual ligand screening, molecular profiling, structural prediction, refinement, and optimization (Roney & Mohd Aluwi 2024). This methodology has become increasingly important in medicin-

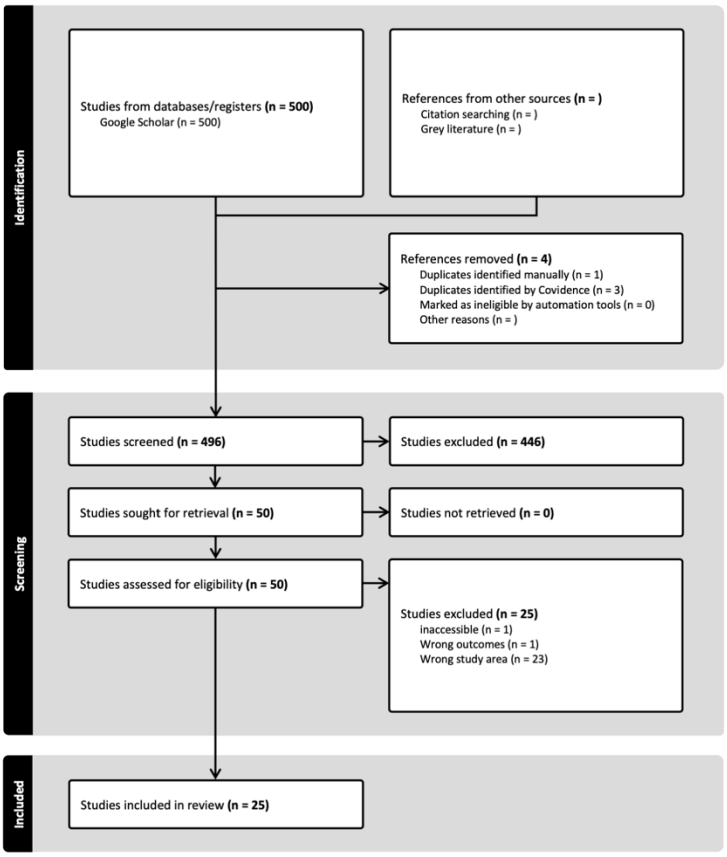

Figure 1. PRISMA flow diagram systematic literature review of *P. crocatum* as antidiabetic

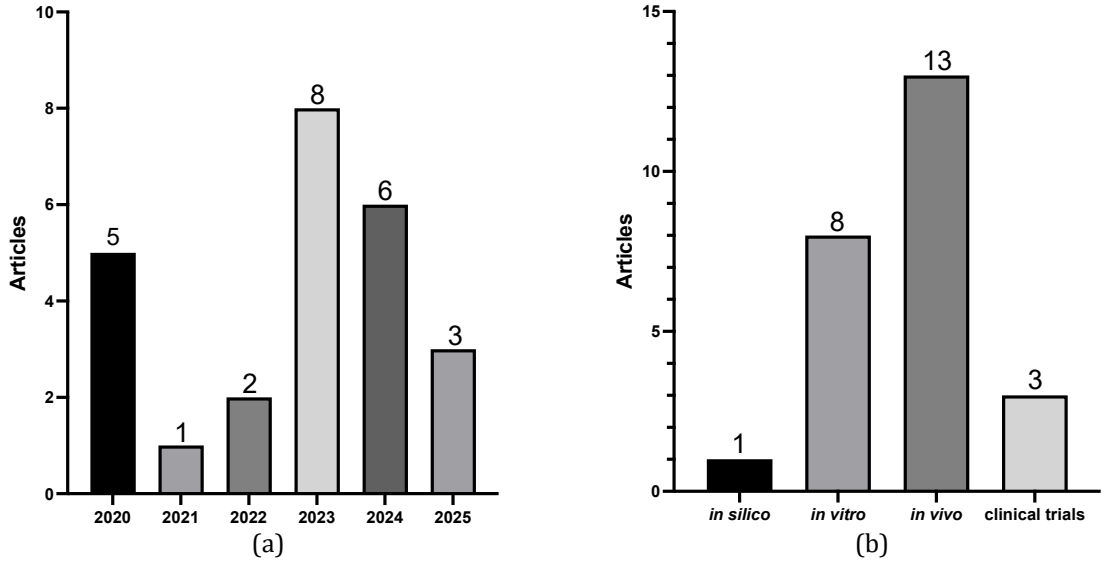

Figure 2. Distribution of articles based on: (a) publication year, (b) experimental model

al chemistry and pharmacology, where it is applied for compound screening, interaction assessments, predictive modeling, and related applications. A key advantage of the *in silico* approach is its reliance solely on computational infrastructure and software, thereby reducing the immediate dependence on experimental systems such as cell-based assays, animal models, or human trials. Nevertheless, because these analyses are primarily guided by scoring algorithms, their capacity to provide precise estimations of binding energies remains

limited. Consequently, confirmatory wet-laboratory experiments are indispensable to substantiate molecular interactions under physiologically relevant conditions (Tessema et al. 2024).

An *in silico* docking study assessed multiple compounds isolated from the ethyl acetate fraction of *P. crocatum* leaves for their potential as α-glucosidase inhibitors. The compounds evaluated comprised ethyl L-serinate hydrochloride, schisandrin B, columbin, 4-(4-methoxy-phenylamino)-2,3-dihydro-1H-4a,9-diazacyclopenta(b)-fluorine-10-carbonitrile, 6-amino-4-[3-(benzyloxy)phenyl]-3-tert-butyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile, 4-{{4,6-bis[(3R,5S)-3,5-diamino-1-piperidinyl]-1,3,5-triazine-2-yl}amino}benzenesulfonamide, and 1,1'-(1,4-butanediyl)bis{2,6-dimethyl-4-[(3-methyl-1,3-benzothiazol-2(3H)ylidene)-methyl]pyridinium}. Among these candidates, columbin demonstrated the greatest binding affinity toward α-glucosidase, indicated by the lowest calculated free binding energy of –9.0 kcal/mol. Molecular docking predicted that columbin interacts with several key amino acid residues, including Ser240, Asp242, His280, Arg315, Glu411, Phe159, Arg442, Tyr158, and Phe303 (Weni, Safithri & Seno 2020).

In Vitro Study

In vitro experimental systems are widely utilized during the preliminary phases of drug discovery and formulation development to estimate the prospective *in vivo* activity of new compounds. Such models present notable benefits, including lower costs relative to *in vivo* investigations, ease of setup, absence of ethical restrictions, and the ability to tightly regulate experimental variables. Nonetheless, several drawbacks exist, such as the absence of authentic intestinal architecture and physiology, potential variability between laboratories, and limited capacity to represent inter-individual differences (Xu et al. 2021). Antidiabetic *in vitro* assays are broadly divided into two principal categories according to target specificity: phenotypic assays and target-based assays. Phenotypic approaches include glucose uptake, reporter gene, insulin secretion, calcium measurement, ATP measurement, and cAMP assays, whereas target-based methods encompass PPARγ and GLUT-4 assays, α-amylase and α-glucosidase inhibition assays, as well as PTP1B assays (Vhora et al. 2020). Eight independent investigations utilized *in vitro* approaches to assess the antidiabetic activity of *P. crocatum*, specifically by examining its inhibitory effects on the enzymes α-amylase and α-glucosidase. A summary of the

Table 1. Reported *in vitro* studies on *Piper crocatum* with relevance to antidiabetic effects

Part of Plants	Method of Extraction	Assay	Result	Ref.
Leaves	Macerate in MeOH	α-Glucosidase	10.013 ± 0.070 mg/mL IC_{50}	(Hartini & Setyaningsih, 2021, 2023)
		α-Amylase	8.463 ± 0.318 mg/mL IC_{50}	
Leaves	Macerate in 70% EtOH	α-Glucosidase	1.29% to 40.80% at concentration 0,1% to 1%	(Alfarabi et al, 2020)
Leaves	Macerate in 70% EtOH, then fractionation using LLE	α-Glucosidase	IC_{50} values: 3808.30 ± 81.25 µg/mL (70% EtOH extract); 3793.50 ± 103.46 µg/mL (n-hexane fraction); 743.80 ± 42.43 µg/mL (EtOAc fraction); 2730.39 ± 353.92 µg/mL (aqueous fraction)	(Weni & Safithri, 2022)
Leaves	Sequential maceration using n-hexane, ethyl acetate, and methanol	α-Glucosidase	At 10.000 ppm, inhibition was 98.07 ± 0.31% (MeOH extract), 31.92 ± 1.11% (EtOAc extract), and 8.86 ± 0.60% (n-hexane extract).	(Abdullah, Seno, & Safithri, 2024)
Leaves	Boiled with distilled water 15 min (infundastion)	α-Glucosidase	0.76±0.12%; 1.11±0.39%; up to 1.43±0.33%.	(Yuniasih, Safithri, & Syaefudin, 2023)
Leaves at 2, 4, 6 and 8 months	Extracted using pressurised hot water extract (PHWE)	α-Glucosidase	• At 5 mg/mL showed 46.65±0.63% (2 months); 75.57±0.44% (8 months). • At 10 mg/mL showed 53.16±1.85% (2 months); 83.81±0.53% (8 months). • At 20 µg/mL showed 82.47±1.16% (2 months); 88.70±0.42% (8 months)	(Kamaruzaman, Kasim, & Jaafar, 2020)
		α-Amylase	• At 5 mg/mL showed 26.67±0.21 % (2 months); 82.84±0.97% (8 months). • At 10 mg/mL showed 40.66±0.24% (2 months); 85.73±0.70 (8 months). • At 20 mg/mL showed 51.83±0.44% (2 months); 87.05±0.64 (8 months).	
Stem	Sequential maceration using n-hexane, ethyl acetate, and methanol	α-Glucosidase	IC_{50} results: MeOH = 6.39 mg/L; EtOAc = 5.27 mg/L; n-hexane = 9.76 mg/L	(Irawan et al., 2024)

findings from these *in vitro* studies is presented in Table 1.

Compared with other members of the genus, including *Piper aduncum*, *P. betle*, and *P. retrofractum*, *P. crocatum* has been reported to exert more pronounced antidiabetic effects (Hartini & Setyaningsih 2023). Among the different samples, the ethyl acetate fraction displayed the strongest α-glucosidase inhibitory activity when compared with 70% ethanol extract, n-hexane, and aqueous fractions (Weni &

Safithri 2022). Conversely, studies employing successive maceration with solvents of increasing polarity indicated that the methanol extract was more active than either the n-hexane or ethyl acetate extracts (Abdullah, Seno & Safithri 2024). The biological activity of *P. crocatum* was also influenced by harvest maturity, with plants collected at eight months showing the highest potency, a result attributed to elevated polyphenolic content that facilitates stronger interactions with carbohydrate-hydrolyzing enzymes, thereby suppressing their catalytic function (Kamaruzaman, Kasim, & Jaafar 2020). In contrast, leaves prepared by infusion (boiling for 15 minutes) exhibited only modest α-glucosidase inhibition (Yuniasih, Safithri & Syaefudin 2023). Mechanistically, inhibition of α-glucosidase reduces the breakdown of polysaccharides into glucose, leading to lower intestinal glucose absorption and attenuation of postprandial hyperglycemia (Muhammad Alfarabi et al. 2020; Sapalma & Ahmad 2024).

In Vivo Study

In vivo assay plays an essential role in preclinical drug development, serving as a key approach for assessing intestinal absorption and the pharmacological performance of drug candidates in living organisms. Despite its importance, this stage of evaluation is both resource-intensive and time-consuming. A range of animal species, such as rats, mice, rabbits, pigs, and dogs, are commonly employed to investigate the efficacy of orally administered formulations (Xu et al. 2021). In the context of antidiabetic studies, experimental models are established to replicate diabetic conditions either through genetic manipulation or induction methods. Because genetically diabetic animals are limited in availability, most *in vivo* antidiabetic investigations rely on induction strategies, including single-agent exposure with alloxan or streptozotocin, combined streptozotocin–nicotinamide protocols, high-fat diet regimens, high-fat diet plus streptozotocin induction, fructose-rich diets, partial pancreatectomy, or intrauterine growth retardation (IUGR) models (Husna et al. 2019). Research exploring the antidiabetic properties of *P. crocatum* has primarily utilized alloxan and streptozotocin-based models, including streptozotocin combined with nicotinamide. Altogether, 13 *in vivo* studies on *P. crocatum* have been reported and are summarized in Table 2.

The hypoglycemic potential of *P. crocatum* has been shown to be comparable to that of standard positive controls (Adrianto et al. 2023; Andrianto, Hujjatusnaini & Nirmalasari 2025; Navirius, Pamudji & Herowati 2023; Utari et al. 2023). Other study revealed that its glucose-lowering activity was more prono-

unced in mice (Sembiring, Nasution & Chiuman Linda 2023) than in rats (Damanik, Manafe & Kareri 2024) under similar alloxan-induced diabetic conditions. Results from *in vivo* experiments were consistent with *in vitro* findings, indicating that polar extracts were more effective than non-polar fractions. This superiority is linked to the higher phenolic content present in polar fractions, notably flavonoids and tannins (Utari et al. 2023). Flavonoids contribute to glycemic control by suppressing carbohydrate-digesting enzymes, enhancing insulin secretion from pancreatic β-cells, and promoting glucose uptake in muscle and peripheral tissues via glucose transporter pathways. Meanwhile, tannins act by stimulating phosphorylation of glucose transport mechanisms and limiting intestinal glucose absorption through mucosal layer formation, thereby strengthening the antidiabetic effect (Rahmatullah, Pangkahila & Budhiarta 2020; Wiliam, Sinaga & Tarigan 2025). Moreover, *P. crocatum* leaves contain 0.7866% quercetin, a bioactive flavonoid that improves insulin sensitivity and inhibits α-glucosidase, further supporting its antidiabetic efficacy (Sapalma & Ahmad 2024).

Clinical Trials

According to the National Institutes of Health (NIH), a clinical trial is defined as a study involving one or more human participants, aimed at generating biomedical or behavioral outcomes related to health (Zhang & Yang 2024). Research on *P. crocatum* has reached the stage of human application, supported by its traditional use as an antidiabetic remedy among certain ethnic groups (Damanik, Manafe & Kareri 2024). The plant is typically administered as a decoction of its leaves. In 2023, a trial was conducted in patients with diabetes mellitus at Setia Janji Health Center, where daily administration of *P. crocatum* leaf decoction for 7 days (morning and afternoon) reduced blood glucose levels to below 200 mg/dL, with an average post-treatment value of 183.15 mg/dL and a mean reduction of 82.90 mg/dL compared with baseline (Pane, Suryantara & Kristiarini 2023). A subsequent report in 2024 confirmed similar outcomes at UPDT Puskesmas Gunungsitoli Utara, where patients receiving *P. crocatum* leaf decoction also experienced significant glucose reduction (Amazihono & Waruwu 2024). In 2025, further evidence was provided from studies at Padangsari and Srondol Health Centers in Semarang, demonstrating that administration of *P. crocatum* leaf extract for 7 days lowered fasting blood glucose by an average of 68.6 mg/dL, corresponding to a 37.81% reduction an effect superior to that of the control group not receiving the extract (Wigatiningtyas et al. 2025). Collectively,

Table 2. Overview of *in vitro* assessments of the antidiabetic potential of *Piper crocatum*

Method of extraction	Animals	Induction	Dosage	Result	Ref.
Macerate in 96% EtOH	Rats	Streptozotocin 40 mg/kg BW	150, 250, and 350 mg/kg BW	Administration at 150 mg/kg BW resulted in the most pronounced reduction in rat blood glucose, with a mean decrease of 238.25 mg/dL	(Tandi, et al. 2020)
Macerate in 96% EtOH	Rats	Alloxan 140 mg/kg BW	150, 250, and 350 mg/kg BW	Following alloxan induction, peak hyperglycemia occurred on day 18. Red betel leaf extract lowered glucose by 84.6 mg/dL (45.83%) at 150 mg/kg BW, 250.2 mg/dL (67.88%) at 250 mg/kg BW, and 163.8 mg/dL (49.52%) at 350 mg/kg BW, with 250 mg/kg BW showing the greatest effect.	(Damanik et al., 2024)
Macerate in 95% EtOH	Rats	Streptozotocin 60 mg/kg BW and nicotinamide 120 mg/kg BW	125, 250, and 500 mg/kg BW	Blood glucose declined by day 31 in glibenclamide and red betel extract groups, with the greatest reduction on day 39. Significant differences ($p < 0.05$) were observed between negative control, positive control, and 500 mg/kg BW extract, which showed a glucose-lowering effect comparable to the positive control.	(Navirius, Pamudji, & Herowati, 2023)
Macerate in 96% EtOH, then fractionation to get the polar and non-polar fraction	Rats	Alloxan 150 mg/kg BW	2%	Polar fraction reduced glucose by 194.4 mg/dL (69.18%) on day 14, nearly matching glibenclamide with decrease of 204.9 mg/dL (74.37%), while the non-polar fraction showed a 100 mg/dL (39.90%) reduction.	(Utari, et al. 2023)
Macerate in 70% EtOH	Rats	Alloxan 120 mg/kg BW	100, 200, and 400 mg/kg BW	On day 21, red betel leaf extract lowered rat blood glucose by 53.76% (72.88 mg/dL) at 100 mg/kg BW, 60.07% (85 mg/dL) at 200 mg/kg BW, and 65.29% (106.21 mg/dL) at 400 mg/kg BW.	(Widiana & Marianti, 2022)
Macerate in 70% EtOH	Rats	Streptozotocin 45 mg/kg BW dan nicotinamide 110 mg/kgBW	50, 100, and 200 mg/kg BW	Red betel leaf extract at 100 and 200 mg/kg BW lowered blood glucose significantly, showing no difference from glibenclamide. The ethanol extract at 100 mg/kg BW was the most effective, producing an 18.22% reduction.	(Adrianto et al., 2023)

Table 2 (continue). Overview of *in vitro* assessments of the antidiabetic potential of *Piper crocatum*

Method of extraction	Animals	Induction	Dosage	Result	Ref.
Macerate in 70% EtOH	Rats	Alloxan 150 mg/kg BW	50, 100, and 200 mg/kg BW	After 14 days, red betel leaf extract lowered blood glucose by 134.34 mg/dL (31.30%) at 50 mg/kg BW, 162.67 mg/dL (62.68%) at 100 mg/kg BW, and 138.16 mg/dL (66%) at 200 mg/kg BW.	(Sapalma & Ahmad, 2024)
Macerate in 70% EtOH	Rats	Alloxan 125 mg/kg BW	2%, 4%, and 6%	After 24 days, red betel leaf extract lowered rat blood glucose by 69.33 mg/dL (32.50%) at 2%, 77.33 mg/dL (34.94%) at 4%, and 144.67 mg/dL (61.65%) at 6%.	(Susanti, Gusfarenie, & Nuraida, 2024)
Decoction in water	Rats	Alloxan 4.76 mg/20gr BW	0.4 mL/20g BW and 0.5 mL/20g BW	Decoction of red betel leaf (*Piper crocatum*) at 0.4 and 0.5 mL/20 g BW lowered blood glucose in diabetic male mice (*Mus musculus*), with the 0.5 mL/20 g BW dose showing the greatest effect.	(Wiliam, Sinaga, & Tarigan, 2025)
NI*	Rats	Streptozotocin 13mg/200g BW and nicotinamide 46mg/200g BW	0.6 g/200gBB/day	Treatment with *Piper crocatum* leaf extract lowered fasting blood glucose by 39.38 ± 13.36 mg/dL, though the effect was less pronounced than metformin.	(Rahmatullah, Pangkahila, & Budhiarta, 2020)
Boiled in distilled water and blended with ginger and cinnamon extracts (42:25:33)	Rats	Streptozotocin 50 mg/kg BW	9 mL/kg bw and 13.5 mL/kg bw	After 14 days, red betel combination extract reduced rat blood glucose by 18–55% versus the diabetic control (aquadest). The greatest reduction, 55.42%, was observed at 9 mL/kg BW.	(Safithri, Bintang, et al., 2023)
Macerate in 96% EtOH	Mice	Alloxan 150 mg/kg BW	100, 300, and 500 mg/kg BW	At 100 mg/kg BW, red betel extract lowered blood glucose by 58.78% (from 409 to 168.6 mg/dL), followed by 300 and 500 mg/kg BW.	(Sembiring, Nasution, & Chiuman Linda, 2023)
Macerate in 96% EtOH	Female mice	Alloxan 0.6mL/day	Combination of *Piper crocatum* and *Tinospora crispa* (3:2) at concentrations of 20%, 40%, 60%, and 80%.	The strongest antihyperglycemic effect was observed at the lowest concentration (20%), as higher concentrations (40%, 60%, 80%) showed no difference as 20%. Concentration of 20% was statistically comparable to the positive control (metformin)	(Andrianto, Hujjatusnaini, & Nirmalasari, 2025)

Note: NI* - No Information

these reports indicate that clinical studies of *P. crocatum* show clear hypoglycemic effects in humans, supporting its potential for downstream development as a herbal product to complement conventional antidiabetic therapies.

CONCLUSION

Evidence from *in silico*, *in vitro*, *in vivo*, and clinical investigations consistently supports the glucose-lowering potential of *P. crocatum*. Based on *in silico* study, columbin demonstrated the greatest binding affinity toward α-glucosidase. *In vitro* experiments revealed that the ethyl acetate extract of *P. crocatum* stem exhibited the greatest α-glucosidase inhibitory activity, whereas the methanol leaf extract showed the strongest α-amylase inhibition. *In vivo* studies demonstrated that doses of 100–250 mg/kg BW significantly lowered blood glucose under diverse conditions and animal models. Moreover, clinical trials indicated that twice-daily administration of the decoction for a minimum of seven days effectively reduced blood glucose levels in diabetic patients. Overall, the available studies position this species as a promising natural antidiabetic candidate. Future research should focus on translating these findings into the development of herbal-based antidiabetic products through downstream innovation. In particular, formulation studies are essential to advance *P. crocatum* toward recognition as Standardized Herbal Medicine (OHT) and Phytopharmaceutic.

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