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## Potential for Blood Glucose Reduction by Indonesian Plant Leaf Extracts: Systematic Review of in Vivo Studies

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### Abstract

Introduction: Diabetes mellitus is a chronic disease characterized by persistent hyperglycemia. The rising prevalence of diabetes has increased interest in alternative therapies, including herbal medicines. Indonesia has abundant medicinal plants whose leaf extracts contain bioactive compounds with potential antidiabetic effects, yet scientific evidence regarding their effectiveness remains fragmented. Purpose: Therefore, this study aims to systematically review the potential of Indonesian plant leaf extracts in reducing blood glucose levels based on in vivo experimental studies. Method: A systematic review was conducted by following the PRISMA guidelines through a literature search on the Google Scholar and Science Direct databases. The articles analyzed were original studies published between 2020 and 2025 that focused on in vivo studies examining the potential of various leaf extracts to reduce blood glucose levels. Discussion: Phytochemical analysis indicates that leaf extracts may act effectively by providing antioxidant protection to pancreatic beta cells, increasing GLUT4 expression, and inhibiting digestive enzymes. Although their effects can rival standard drugs with a lower risk of hypoglycemia, the current literature still has limitations, particularly the short duration of in vivo testing and the lack of chronic toxicity data. Conclusion: Indonesian plant leaf extracts show promising potential as natural antihyperglycemic agents; nevertheless, further studies involving long-term toxicity evaluation, standardized extraction methods, and clinical trials are required to confirm their safety and effectiveness in humans.

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### Keywords:

p glucose reduction, leaf extract, in vivo, anti-diabetic

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## INTRODUCTION

Diabetes mellitus is one of the chronic non-communicable diseases with an increasing prevalence both in Indonesia and worldwide, and it is one of the main conditions of concern in health services (Maharani, 2022; Pratiwi et al., 2024). According to the International Diabetes Federation (IDF) Atlas 2021, the number of people with diabetes globally in 2024 is estimated to reach 537 million in the 20–79 year age group, and this figure is expected to increase to 783 million by 2045, indicating a rising global disease burden (IDF Diabetes Atlas, 2021). In addition, the prevalence of diabetes in Southeast Asia is reported to be high and continues to increase every year. In Indonesia, the prevalence of diabetes mellitus is also relatively high; Riskesdas 2018 shows an increase from 6.9% to 10.9% in 2018 (Riskesdas, 2018; Widiyari et al., 2021). Besides predicting prevalence globally and nationally, it is also important to predict the risk of diabetes at the individual level in order to reduce the development of diabetes mellitus and prevent complications (IDF Diabetes Atlas, 2021;

Riskesdas, 2018; Widiyanti et al., 2021). This increase in prevalence is generally associated with unhealthy behaviors such as poor diet and eating patterns (high sugar and fat intake), psychological stress, and pancreatic damage. Furthermore, public education and awareness related to diabetes mellitus are still lacking, so many people do not fully understand this disease (Komang Ayuni, 2020; Kadek Diah Purnamayanti et al., 2025).

Diabetes mellitus is typically characterized by chronic hyperglycemia caused by multiple risk factors; for example, type 2 diabetes mellitus is usually the result of a combination of genetic, metabolic, and environmental factors that interact with one another (Suputra, 2024). Other studies also report that diabetes mellitus can lead to decreased cognitive function, reduced sleep quality, and even an increased risk of amputation when complications such as diabetic foot occur (Enrico et al., 2021; Putri et al., 2025; Gede Surya Dinata et al., 2023). These conditions can be managed with lifestyle modifications, including improving sleep quality, as better sleep can positively affect blood glucose levels. However, the most important component of management remains the use of antidiabetic drugs. The use of antidiabetic agents such as insulin and oral antidiabetic drugs (OAD) often carries the risk of side effects, which may reduce patients' quality of life both physically and economically. This situation has encouraged growing interest in complementary and non-pharmacological therapies derived from natural ingredients that can be used as alternatives or adjuncts to pharmacological treatment (Putri et al., 2025; Joddy et al., 2017).

Indonesia has an abundance of herbal plants, and their leaves are commonly studied and used by the community to lower blood glucose levels. Preliminary studies have shown that several leaf extracts contain active compounds such as flavonoids, alkaloids, tannins, and saponins that have the potential to reduce blood sugar through various mechanisms, including inhibition of alpha-glucosidase enzymes or improvement of insulin sensitivity. Although many primary studies have demonstrated the effectiveness of leaf extracts in lowering glucose levels and these findings have been reported in various publications, there are still few works that comprehensively summarize the effectiveness of each tested leaf extract.

Therefore, this systematic review will discuss experimental research on leaf extracts that can lower blood sugar levels through in vivo studies (experimental animals). The aim is to evaluate and summarize the latest scientific evidence from studies conducted between 2020 and 2025. This review was compiled using the PRISMA protocol to provide credible and transparent data. It is expected that this systematic review can serve as a basis for the development of standardized herbal medicines and support holistic treatment for people with diabetes mellitus in the future.

## **METHODS**

This literature review was conducted under the guidelines of Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA). In the literature search, 2 electronic databases were carried out, namely Google Scholar and Science Direct to identify all empirical studies that discuss the Potential for Glucose Reduction by leaf extracts. The articles under review are scientific publications published in the 2020-2025 time frame. The keywords used in the literature search were: (1) leaf extract, (2) blood sugar, (3) in vivo, and (4) Indonesian. These four keywords were combined using Boolean operators to be "leaf

extract" AND "blood glucose" AND "in vivo" AND "Indonesia" and used in English-language searches to expand the scope of relevant studies.

Articles found will be systematically selected with inclusion and exclusion criteria. The inclusion criteria used include articles (1) discussing the Potential for Glucose Reduction by foliage extract; (2) is original research, both observational and interventional studies; (3) available in full *text*; (4) written in Indonesian or discussed in English; (5) issued within the last ten years (2020-2025). The exclusion criteria include (1) articles in the form of opinions, comments, and non-systematic reviews; (2) articles that do not specifically discuss the Potential for Glucose Reduction by Foliage Extract; (3) articles that are not available in full text, and (4) articles that are the same or have the same content as other publications.

The selection process is carried out in stages, starting from identifying the title and abstract, as well as studying the text completely. If there are inappropriate opinions between researchers in the selection process, it will be resolved by involving the supervisor to reach a consensus. Articles that meet the criteria will be extracted key data including: (1) the author's name and year of publication; (2) the name of the leaf used; (3) test animals; (4) induction method; (5) Estrate/solvent type; (6) Main result. All extracted data will be compiled in the form of a synthesis table to facilitate descriptive analysis and comprehensive conclusions.

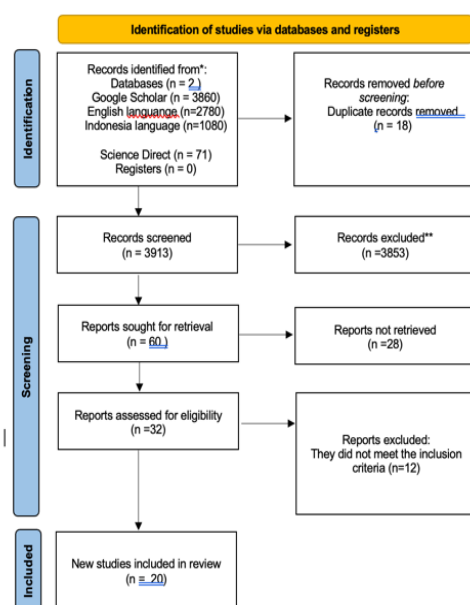


Figure 1. PRISMA Flow Diagram.

Source: Literature search results processed by the author based on PRISMA guidelines (2026)

## RESULTS AND DISCUSSION

**Table 1.** Summary of the In Vivo Study of the Antidiabetic Effect of Indonesian Foliage Ethanol Extract on an Aloxan-Induced Rats Model.

No.	Author (Year)	Plant Name	Test Animal	Induction Method	Types of Extracts	Key Results
1.	Hakim et al. (2024)	Leaf (P. Pellucida)	Rats	São Paulo	Ethanol	Lowers blood glucose and accelerates healing of diabetic ulcer wounds
2.	Lengkong et al. (2024)	Leaf Squirrel (C. Minahassae)	Rats	São Paulo	Ethanol	An extract of 200 mg/kg showed the most significant reduction in glucose
3.	Niam et al. (2024)	Matoa leaf (P. pinnata)	Rats	São Paulo	Ethanol	Prevents weight gain that occurs with glibenclamide
4.	Nasihah (2021)	Ngokilo Leaf (S.mutabilis)	Rats	São Paulo	Ethanol	Effectively lowers the glucose of male white rats significantly
5.	Herlina et al. (2022)	Breadfruit Leaf (A. altilis)	Rats	São Paulo	Ethanol	A 39.91% decrease in glucose and an improvement in pancreatic histology
6.	Sumarlin et al. (2023)	Namnam leaf (C.clauiflora)	Rats	São Paulo	Ethanol	Lowers blood glucose and improves lipid levels (cholesterol)
7.	Mendrofa et al. (2024)	Leaf Cluster (S.Spontanum)	Rats	São Paulo	Ethanol	A dose of 400 mg/kg indicates the most optimal antidiabetic
8.	Liberitera et al. (2023)	Karamunting Leaf (R. Tomentosa)	Rats	São Paulo	Ethanol	Potential blood glucose decrease comparable to positive control
9.	Rollando et al. (2022)	Basil Leaf (A. cordifolia)	Rats	São Paulo	Ethanol	The effectiveness of the dose of 300 mg/kg is consistent with the effect of glibenclamide
10.	Pelu et al. (2021)	Nutmeg Leaf (Mystrica Fragnans)	Rats	São Paulo	Ethanol	A dose of 300 mg/kg provides the best glucose-lowering effectiveness

Source: Data compiled and processed from selected articles (2020–2025)

**Table 2.** Summary of In Vivo Study on Antidiabetic Effects of Indonesian Foliage Ethanol Extract on Alox-Induced Mouse Model

No.	Author	Plant Name	Test	Induction	Types of	Key Results
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(Year)	Animal	Method	Extracts		
1. Asni et al. (2025)	Breadfruit Leaves (A. Communis)	Mint	São Paulo	Ethanol	Lowers blood glucose in mice as the dose increases
2. Aligita et al. (2025)	Leea Indica Leaf	Mint	São Paulo	Ethanol	Effective 400 mg/kg dose supported by molecular interactions at PPAR receptors
3. Solikhah et al. (2020)	Papaya Leaf (C. Papaya)	Mint	São Paulo	Ethanol	Significant decrease in glucose across the entire test dose range
4. Efendi et al. (2021)	Mangrove Leaf (Rhizophora sp)	Mint	São Paulo	Ethanol	Mangrove ethanol extract is effective as a natural antihyperglycemia agent.
5. Sulfiyanti et al. (2023)	Basil Leaf (A.cordifolia)	Mint	São Paulo	Ethanol	70% ethanol extract shows the most stable in vivo activity
6. Solikhah et al. (2021)	Karsen Leaf (M.calabura)	Mint	São Paulo	Ethanol	Lowers Glucose and helps maintain the stability of the mice's weight
7. Hidayat et al. (2021)	Sambiloto Leaf (A.Paniculata)	Mint	São Paulo	Ethanol	Significantly increases the expression of GLUT4 protein in muscle tissue
8. Billi et al. (2024)	Sangkubak Leaf (P. cauliflora)	Mint	São Paulo	Ethanol	A dose of 300 mg/kg is the most effective dose to lower glucose
9. Fitriyasti et al. (2022)	- Squirrel (G. Proucumbens)	Mint	São Paulo	Ethanol	Blood glucose-lowering activity begins to be noticeable at a dose of 200 mg/kg
10. Febrina et al. (2021)	Babandotan leaf (A. conycoides)	Mint	São Paulo	Ethanol	Lowers glucose and improves clinical symptoms (drinking volume and urine)

Source: Data compiled and processed from selected articles (2020–2025)

### **Efficacy of Various Indonesian Plant Foliage Extracts**

The search of various literature with in vivo studies provides an interesting finding, where these studies reveal a very wide spectrum of leaf efficacy for glucose reduction in

Indonesia. Plants that can exert a hypoglycemic effect are not dominated by a single botanical family but are found across multiple botanical families. Plants that commonly grow in household yards, such as the leaves of seruhan (*Peperomia pellucida*), breadfruit leaves (*Artocarpus communis*), papaya leaves (*Carica papaya* L.), and kersen leaves (*Muntingia calabura* L.), have shown significant hypoglycemic potential. Not only yard plants, but also perennial and spice plants such as matoa leaves (*Pometia pinnata*) and nutmeg leaves (*Myristica fragrans*) demonstrate high effectiveness in normalizing blood glucose levels in diabetogenic-induced animals. In addition, coastal plants such as mangrove species (*Rhizophora* sp.) and terrestrial weeds such as babandotan (*Ageratum conyzoides* L.) also exhibit similar benefits. These findings indicate that bioactive compounds capable of lowering glucose levels are not limited to specific plant families but are widely distributed within Indonesia's biodiversity (Pelita Hakim et al., 2024) (Ode Nur Asni & Sri Rahayu, 2025) (Solikhah et al., 2020) (Solikhah & Solikhah, 2021) (Labib et al., 2024) (Aulia et al., 2021) (Efendi et al., 2021) (Mira Febrina et al., 2023).

Each plant has a different level of effectiveness; however, based on the overall results of the review, the effectiveness observed is highly dependent on the administered dose (dose-dependent). For example, in the leaves of karamunting (*Rhodomyrtus tomentosa*), sengkubak (*Pycnarrhena cauliflora*), and namnam (*Cynometra cauliflora*), the reduction in glucose levels was shown to be very significant as the dose increased in experimental animals. This decrease generally occurs linearly until the leaf extract reaches its maximum efficacy threshold, which is almost comparable to the performance of positive control drugs (Liberitera et al., 2023) (Billi et al., 2024) (Hidayat & Hayati, 2020).

Plants that have long been used in traditional medicine practices, such as sambiloto leaves (*Andrographis paniculata*), binahong leaves (*Anredera cordifolia*), and life extension leaves, demonstrate stable performance in producing hypoglycemic effects. Testing using mice and rats provides evidence that Indonesian plant leaf extracts have empirical effects that align with laboratory findings. The high success rate observed in various plant species may serve as a strong preclinical foundation. This indirectly confirms that Indonesian leaf extracts possess sufficient scientific feasibility to be advanced to the next stage, including phytopharmaceutical standardization, toxicity profile determination, and the design of clinical trials as complementary agents in diabetes therapy (Hidayat & Hayati, 2020) (Rollando et al., 2022) (Fitriyasti et al., 2022).

#### Mechanism of Action of Phytochemicals in Lowering Blood Glucose

Leaf extracts from Indonesian plants are highly effective in controlling blood glucose levels in the body. Their effectiveness is closely related to the richness of secondary metabolites such as flavonoids, alkaloids, tannins, and saponins. Based on the results of previous reviews, most in vivo tests used alloxan induction as an anti-diabetogenic model. Therefore, phytochemical analysis can be categorized based on the body's response to alloxan induction. Alloxan induction specifically produces hyperglycemic conditions through the formation of Reactive Oxygen Species (ROS), which leads to damage and necrosis of pancreatic beta cells (Sulfianti et al., 2023; Tiara Salsabilla Mendrofa & Asyrun Alkhairi Lubis, 2024) (Mira Febrina et al., 2023; Solikhah et al., 2020).

The pharmacological pathway most frequently discussed in the literature is the protection and repair of pancreatic beta cells through antioxidant activity. Flavonoid compounds play an important role as free radical scavengers by donating hydrogen atoms to ROS in the oxidation chain. When this oxidative chain is interrupted, ROS can be neutralized effectively while simultaneously preventing the expansion of pancreatic tissue damage. Antioxidant protection from flavonoid compounds provides an opportunity for pancreatic beta cells to partially regenerate, thereby enabling insulin synthesis and secretion to resume functioning (Liberitera et al., 2023; Ode Nur Asni & Sri Rahayu, 2025) (Lengkong et al., 2023; Solikhah & Solikhah, 2021).

In addition to pancreatic protection from ROS, another mechanism that has been identified is increased glucose uptake in peripheral tissues, which is an essential process in reducing insulin resistance. Specific studies have demonstrated that the administration of leaf extracts rich in secondary metabolites can stimulate increased expression of the transporter protein GLUT4 in peripheral muscle tissue cells (Hidayat & Bio). This increase in GLUT4 expression can indirectly enhance cellular sensitivity in absorbing glucose from the bloodstream. These findings are consistent with the results of molecular docking (in silico) and in vitro tests showing that active plant compounds possess strong binding affinity with insulin-regulating receptors, thereby facilitating glucose translocation (Aligita et al., 2025; Sulfianti et al., 2023).

The literature also indicates additional mechanisms that mimic the action of oral hypoglycemic drugs, namely the inhibition of carbohydrate-digesting enzymes. Certain phytochemical compounds such as tannins and alkaloids have been shown to inhibit the activity of glucosidase and amylase enzymes in the gastrointestinal tract. The inhibition of these enzymes slows the breakdown of complex carbohydrates, thereby delaying and reducing the rate of glucose absorption in the small intestine. This delay in absorption directly contributes to reducing the risk of postprandial blood glucose spikes after meals (Fitriyasti et al., 2022; Sumarlin et al., 2023) (Aulia et al., 2021).

These findings confirm that the secondary metabolites in Indonesian leaf extracts function through multiple pathways. The compounds present can act synergistically as pancreatic-protective antioxidants, enhancers of GLUT4 sensitivity, and inhibitors of digestive enzymes. Therefore, Indonesian plant leaf extracts represent highly comprehensive therapeutic candidates for diabetes management.

#### Critical Evaluation of In Vivo Parameters

From the results of the review, a polarization in the selection of experimental animal models can be observed, with studies almost evenly divided between the use of rats (*Rattus norvegicus*) and mice (*Mus musculus*). The Wistar and Sprague Dawley strains dominate studies using rat models, such as in the testing of extracts from suruhan leaves, leilem leaves, matoa leaves, ngokilo leaves, breadfruit leaves, namnam leaves, gelagah leaves, karamunting leaves, nutmeg leaves, and binahong leaves. Testing with rat models offers the advantage of better physiological stability for repeated observations, with larger blood volumes available for serial blood sampling without triggering excessive hypovolemic stress (Pelita Hakim et al., 2024) (Anastasya Gratia Lengkong et al., 2023) (Labib et al., 2024) (Nasihah, 2021)

(Simanjuntak & Gurning, 2020) (Sumarlin et al., 2023) (Tiara Salsabilla Mendrofa & Asyrun Alkhairi Lubis, 2024) (Liberitera et al., 2023) (Aulia et al., 2021) (Rollando et al., 2022).

Other studies have chosen to use white mice. This selection was reported in evaluations of breadfruit leaves (Ode Nur Asni & Sri Rahayu, 2025), *Leea indica* leaves (Aligita et al., 2025), papaya leaves, mangrove leaves, binahong leaves, kersen leaves, sambiloto leaves, sengkubak leaves, life extension leaves, and babandotan. From a pharmacokinetic perspective, mice possess a much faster basal metabolic rate than rats (Solikhah et al., 2020) (Efendi et al., 2021) (Sulfianti et al., 2023) (Solikhah & Solikhah, 2021) (Hidayat & Hayati, 2020) (Billi et al., 2024) (Fitriyasti et al., 2022) (Mira Febrina et al., 2023). This aspect needs to be critically considered because the significantly higher reduction in blood glucose observed in mice does not necessarily indicate the same strong hypoglycemic effect in humans. Therefore, standardized dose conversion, particularly the Human Equivalent Dose (HED), must be carefully calculated while considering the specific rodent species used.

In this review, all studies relied on intraperitoneal induction of alloxan monohydrate to create hyperglycemic animal models. The use of alloxan in leaf extract testing requires careful evaluation. Alloxan rapidly damages pancreatic beta cells through the formation of Reactive Oxygen Species (ROS). However, alloxan possesses a narrow therapeutic–toxic window. If the administered dose is not appropriate, experimental animals may experience spontaneous recovery (natural regeneration of beta cells within several days), which can introduce research bias. Some studies report that certain leaf extracts, such as gelagah or kersen, successfully reduce glucose levels significantly. However, it remains difficult to determine whether these improvements are entirely due to phytochemical intervention or partly due to spontaneous pancreatic recovery caused by unstable alloxan induction (Solikhah & Solikhah, 2021; Tiara Salsabilla Mendrofa & Asyrun Alkhairi Lubis, 2024).

The most prominent methodological gap identified in the 20 evaluated journals is the relatively short observation duration. Most studies monitor glucose reduction effects only within the acute to subacute testing range, generally between 7 and 14 days, with extract administration conducted consecutively. Diabetes mellitus is a chronic condition that requires long-term treatment, often lifelong. Although Indonesian plant leaf extracts have demonstrated significant glucose-lowering effects in short-term studies, comprehensive long-term toxicity assessments—such as liver function tests (SGOT/SGPT) and kidney function tests (urea/creatinine) after 3–6 months of extract consumption—have not yet been widely reported. The absence of toxicity data (safety profile) represents a fundamental limitation of current in vivo research (Aulia et al., 2021; Fitriyasti et al., 2022; Solikhah & Solikhah, 2021).

#### Comparison of Extract Efficacy with Standard Drugs

To evaluate the clinical feasibility of phytopharmaceutical agents, the most rational benchmark is to compare their effects directly with conventional Oral Hypoglycemic Drugs (OHD). A review of in vivo experimental studies indicates that glibenclamide (a sulfonylurea drug) and metformin (a biguanide) are consistently used as positive control groups. These two standard drugs provide a benchmark for assessing the extent to which leaf extracts can approximate the hypoglycemic potency of synthetic drugs.

Administration of plant extracts at the highest dose ranges generally produces hypoglycemic effects, although they do not always surpass the glucose-lowering potential of standard medications. For instance, analysis of nutmeg leaf extract (*Myristica fragrans*) revealed that a dose of 300 mg/kg body weight produced the most effective blood glucose reduction compared to lower doses. However, its effect still did not exceed the performance of glibenclamide. Similar efficacy patterns—comparable but generally slightly below the positive control threshold—were also reported in in vivo tests of papaya leaf extract (*Carica papaya* L.), sengkubak leaves (*Pycnarrhena cauliflora*), and babandotan leaves (*Ageratum conyzoides* L.) (Aulia et al., 2021) (Solikhah et al., 2020) (Billi et al., 2024) (Mira Febrina et al., 2023).

Studies using metformin as a comparator were conducted in tests of sambiloto (*Andrographis paniculata*) leaf extract, yielding promising results. Sambiloto extract administered at doses of 100 mg/kg body weight and 200 mg/kg body weight produced blood glucose-lowering effects that closely approached the performance of metformin at a dose of 45 mg/kg body weight (Hidayat & Hayati, 2020). These findings suggest that, at certain dose thresholds, the concentration of secondary metabolites within a single extract may rival the efficacy of synthetic drugs.

Although the rate of glucose reduction produced by plant extracts does not always exceed that of synthetic drugs, plant extracts demonstrate advantages in safety regulation. Standard medications such as glibenclamide may stimulate insulin secretion excessively, which can lead to complications such as hypoglycemia (blood glucose levels dropping below normal) and uncontrolled weight gain. However, when the approach shifts toward combination therapy, interesting findings emerge. The literature indicates that simultaneous administration of matoa leaf extract (*Pometia pinnata*) with glibenclamide induction produces a protective synergistic effect. The intervention of matoa leaf extract significantly reduces the risk of extreme hypoglycemia caused by glibenclamide while maintaining the stability of body weight in experimental rats (Labib et al., 2024).

These findings provide a new perspective on the direction of plant pharmacological development. Indonesian plant leaf extracts appear to offer a more adaptable rhythm of glucose reduction, lowering hyperglycemia without forcing glucose levels to drop to life-threatening levels. These characteristics position local plant leaf extracts not merely as substitutes for existing standard drugs but as ideal complementary therapeutic candidates. Consequently, the dosage of synthetic drugs may potentially be reduced in the future, thereby lowering the workload on filtering organs and minimizing the risk of long-term toxicity.

## **CONCLUSION**

This systematic review confirms that Indonesian plant foliage extracts possess very strong hypoglycemic and antihyperglycemic potential. This potential is reinforced by the high content of secondary metabolites such as flavonoids, alkaloids, tannins, and saponins. Pharmacologically, these phytochemical compounds have been shown to provide a comprehensive dual mechanism. The foliage extract is able to act as an antioxidant agent that can restore pancreatic beta cell damage caused by free radical attacks, increase the sensitivity

of glucose uptake in peripheral tissues through GLUT4 expression, and function as an inhibitor of digestive enzymes that delay carbohydrate absorption in the intestine.

When compared with standard oral hypoglycemic drug interventions, Indonesian plant foliage extracts demonstrate comparable glucose-lowering effects at the highest dose range. The advantage of phytopharmaceutical agents lies in their adaptable regulatory rhythm, which allows them to minimize the risk of side effects such as extreme hypoglycemia and drastic weight loss associated with the use of single synthetic drugs. Therefore, Indonesian plant extracts have strong potential to be positioned as ideal complementary therapeutic candidates in the management of Diabetes Mellitus.

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