



Antidiabetic medicinal plants of Indonesia: their in silico, in vitro, in vivo and clinical trial studies

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Abstract The tropical islands of Indonesia house the second largest biodiversity in the world. For generations, indigenous communities have relied on medicinal plants to treat various ailments, including diabetes. However, no comprehensive systematic review has been conducted to consolidate research progress in this area. This review aims to investigate and summarize the current research landscape on antidiabetic medicinal plants in Indonesia. Data collection, collation and analysis were performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Relevant publications on the antidiabetic evaluation of Indonesian medicinal plants were retrieved from leading scientific databases, including **Scifinder®** and **Garuda**, yielding a total of 108 eligible articles. Several notable compound screening studies identified

bioactive phytochemicals with significant antidiabetic potential, such as quinine as a SIRT1 activator, prunetin as an aldose reductase inhibitor, gallic acid as a pancreatic α -amylase (PPA) inhibitor, oleanolic acid as a PTP1B inhibitor, and 3,4,5-tri-*O*-caffeoylquinic acid methyl ester as an α -glucosidase inhibitor. Additionally, clinical investigations and community-based trials reported significant blood glucose-lowering effects from botanical extracts including *Piper crocatum*, *Moringa oleifera*, and *Curcuma xanthorrhiza* in diabetic patients. Recognizing the therapeutic potential of indigenous botanicals, the Indonesian government has intensified its support for the development of scientifically standardized herbal medicines aimed at diabetes treatment, positioning them as part of the country's integrated healthcare system.

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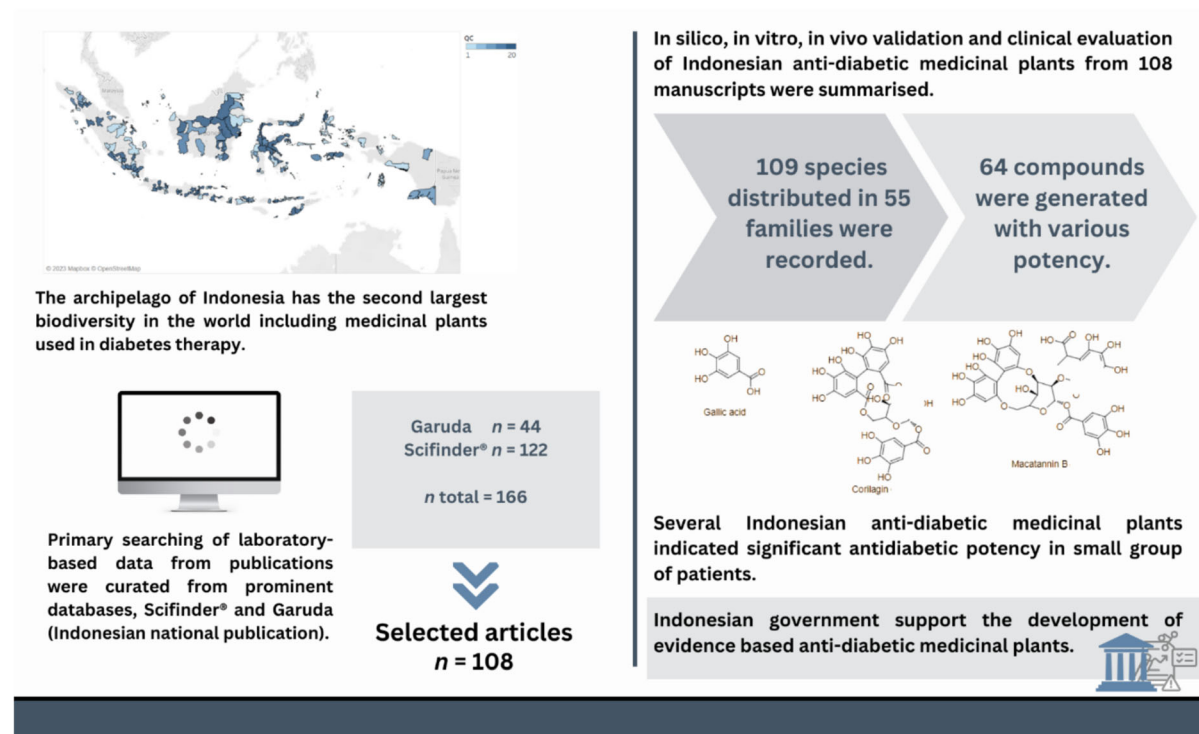
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Graphical abstract



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Introduction

Diabetes is a chronic disease characterized by either the pancreas' inability to produce sufficient insulin or the body's inability to effectively utilize the insulin it produces. There are three main types of diabetes: Type 1 diabetes (T1D), Type 2 diabetes (T2D), and Gestational diabetes (GD) (WHO 2023). While T1D is not preventable, the onset of T2D and GD can often be delayed or prevented through appropriate lifestyle modifications. Poor dietary habits, physical inactivity, and other aspects of an unhealthy lifestyle contribute to metabolic dysfunction, which can lead to degenerative diseases such as diabetes and its hallmark symptom, hyperglycemia (Ratnadewi et al. 2020). According to the International Diabetes Federation (IDF), in 2021, the global prevalence of diabetes was estimated at 537 million people aged 20–79 years, with annual healthcare costs reaching 1 trillion US dollars (IDF 2021). Alarmingly, this figure is projected to rise to 637 million within the next two decades (IDF 2021). Within Southeast Asia, the prevalence of diabetes ranks third globally, and Indonesia ranks fifth in the world, with approximately 19.5 million cases (IDF 2021). This data highlights diabetes as a critical public health concern, affecting not only adults but an increasing number of younger individuals, with the prevalence in Indonesia increasing annually (IDF 2021) (O'Rourke et al. 2020). Beyond its health implications, diabetes imposes substantial socio-economic burdens, diminishing national productivity and quality of life while significantly increasing healthcare expenditures. The worldwide diabetes epidemic is primarily driven by T2D, which is characterized by impaired insulin action and/or abnormal insulin secretion (American Diabetes Association 2020). The initial metabolic abnormality typically involves insulin resistance in key tissues such as muscle, liver, and adipose tissue, resulting in a reduced cellular response to insulin. Alternatively, the defect may manifest at a systemic level, where the blood glucose-lowering effect of both endogenous and exogenous insulin is diminished (Taylor 2012; Roberts et al. 2013). In addition to insulin, several pharmacological classes of glucose-lowering agents are in the management of diabetes, including insulin sensitizers and secretagogues (such as sulfonylureas and meglitinides), thiazolidinediones, α -glucosidase inhibitors, and newer drug modalities such as incretin-based

therapies (DPP-4 inhibitors and GLP-1 receptor agonists), amylin analogues, SGLT-2 inhibitors, bile acid sequestrants, dopamine-2 agonists (Roberts et al. 2013; Meneses et al. 2015; Association 2020). Commonly prescribed drugs such as metformin, sulfonylureas and semaglutide (Ozempic®), which is also approved for weight loss, are frequently utilized in T2D management. However, these treatments are often associated with adverse effects, including transient edema, inflammation, and fat hypertrophy, and gastrointestinal disturbances (Roberts et al. 2013). Moreover, there remains no definitive cure for T1D. An alternative therapeutic approach involves targeting carbohydrate hydrolyzing enzymes, particularly α -amylase, which plays a crucial role in the breakdown of polysaccharides into simpler sugars (Tamarai et al. 2019). The synthetic α -amylase inhibitor **acarbose** has become a standard antidiabetic agent within this class. Despite its efficacy in reducing postprandial hyperglycemia, acarbose is associated with notable gastrointestinal side effects, including flatulence, diarrhea, abdominal bloating, discomfort, and, in rare cases, hepatitis (Cantley and Ashcroft 2015).

Empirical-based herbal treatments for diabetes have been widely practiced in many countries and are often associated with low toxicity and minimal side effects (Ratnadewi et al. 2020; Nisar et al. 2017). As an archipelagic nation with the second largest biodiversity in the world, Indonesia possesses a rich repository of medicinal plants used for managing diabetes. Home to over 300 ethnic groups, Indonesia's diverse cultural heritage includes a wealth of, and rich herbal medicine traditions passed down through generations. A significant initiative, the RISTOJA survey project, spearheaded by the Ministry of Health of the Republic of Indonesia, successfully curated 2,256 medicinal plant species through consecutive programs conducted in 2012, 2015 and 2017 (B2P2TOOT 2012; 2015; 2017). Among these, 250 species were specifically recorded as being traditionally used for diabetes therapy across various regions of the country (Fig. 1). In recent years, Indonesian pharmaceutical companies have increasingly turned to traditional knowledge as a foundation for antidiabetic drug discovery (Tjokroprawiro et al. 2016). For example, studies on *Lagerstroemia speciosa* and *Cinnamomum burmannii* revealed that their bioactive extracts can ameliorate insulin resistance by restoring insulin receptor phosphorylation (Tjokroprawiro et al.

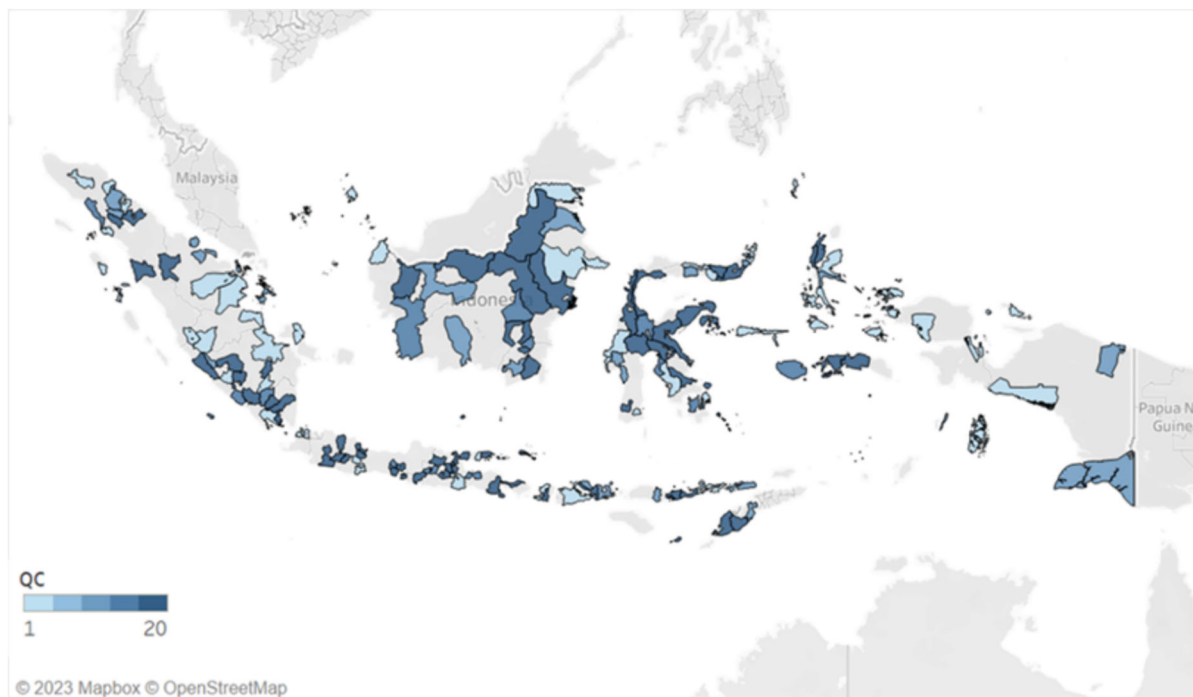


Fig. 1 Map of Indonesia illustrating the distribution density of reported medicinal plants traditionally used for diabetes therapy and management by indigenous communities across the

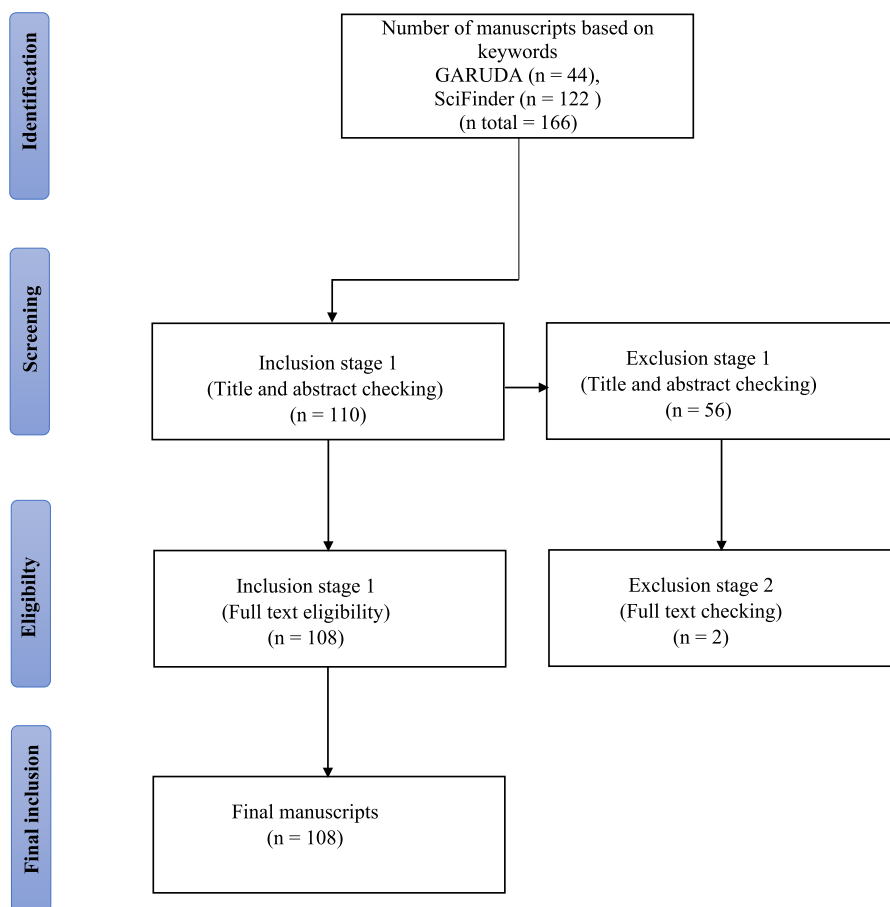
archipelago. Darker blue regions indicate a higher prevalence of herbal medicines use for diabetes treatment

2016). These extracts were also found to enhance GLUT-4 (glucose transporter) translocation from the cytoplasm to the membrane, upregulate PPAR γ , thereby resulting new GLUT-4 synthesis, and suppress TNF- α induced by lipolysis—mechanisms crucial for improving glucose homeostasis (Tjokropawiro et al. 2016). In addition, research on bitter melon fruit (*Momordica charantia*) showed that its nonpolar extract fractions can significantly stimulate insulin secretion from pancreatic beta cells, highlighting its therapeutic potential as a natural antidiabetic agent (Shimada et al. 2022).

Despite these promising studies, no comprehensive review has yet been published on the bioprospecting of Indonesian medicinal plants for antidiabetic applications. In this review, a systematic and literature-based approach was undertaken involving data curation, collation, analysis and discussion to provide new insights into ethnopharmacological practices of antidiabetic therapy across the Indonesian archipelago. An intensive literature mining was conducted using two major databases, Scifinder® (www.scifinder-n.cas.org) and Garuda (www.garuda.kemdikbud.go.id), the

national database of scholarly publications managed by the Ministry of Education, Culture, Research and Technology of the Republic of Indonesia. Standard English keywords included Indonesia AND medicinal plants or Herbs AND diabetes or hyperglycemia. Indonesian search terms such as herbal or *tanaman obat* or *Jamu* AND diabetes or *kencing manis* or *hiperglikemik*. Additionally, specific keywords related to computational studies, enzyme-based evaluation, in vitro and in vivo antidiabetic evaluation and clinical validation of Indonesian medicinal plants were incorporated into the search strategy. Through this systematic literature mining process, a total of 166 articles published between 1990 and 2023 were initially retrieved (Fig. 2). Studies lacking essential information, particularly incomplete data on plant identity or therapeutic use were excluded. Ultimately, 108 articles containing full-text data met the inclusion criteria and formed the basis for data curation, analysis, and the findings discussed in this review.

Fig. 2 Flow diagram of the systematic literature search and selection process for studies on Indonesian antidiabetic medicinal plants, conducted using Scifinder® and Garuda databases



Plant families, mode of uses and scientific studies reported by 108 articles

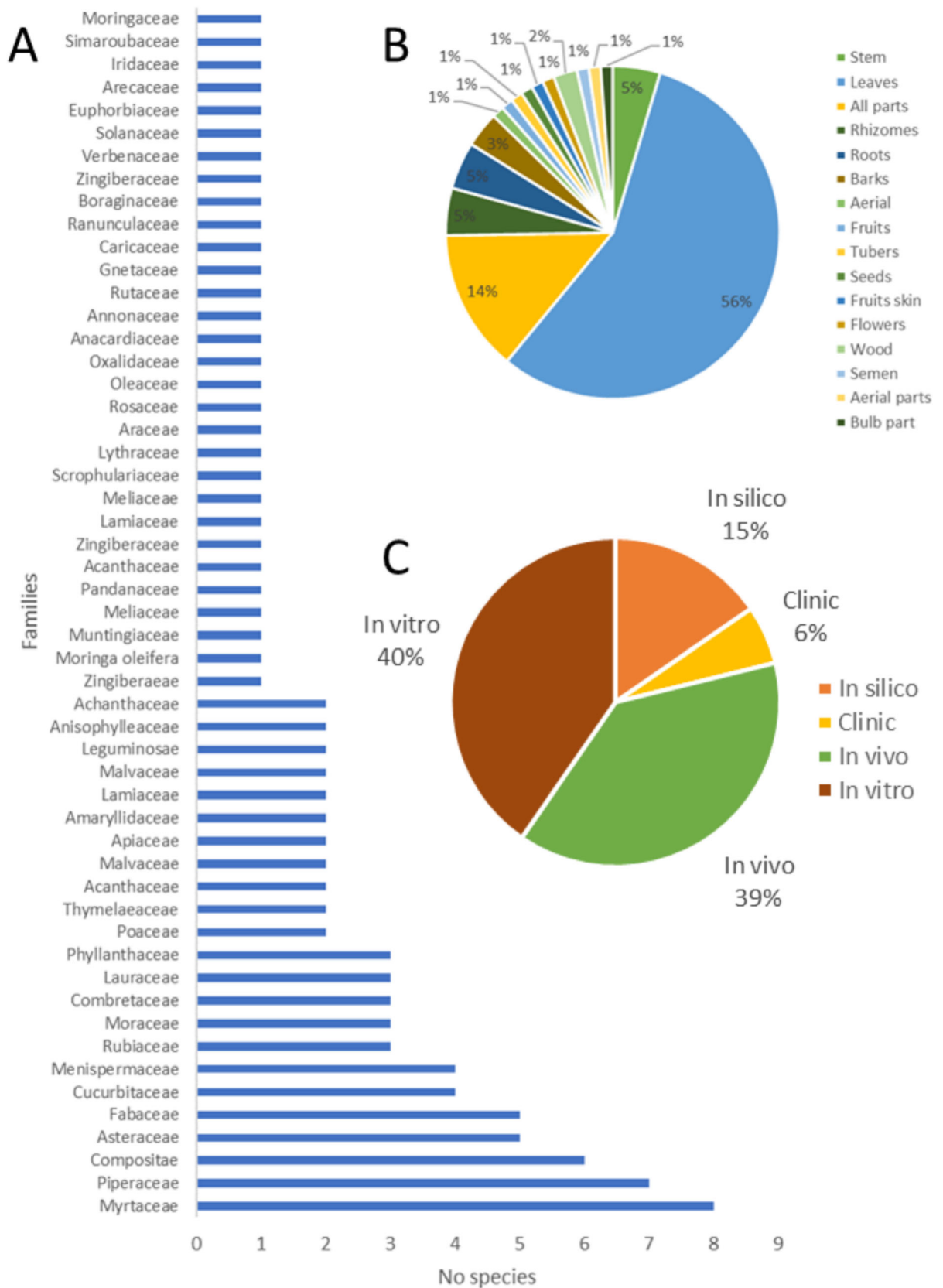
A meta-analysis of 108 full-text articles, covering 109 species of medicinal plants, revealed that these species belonged to a total of 55 families (Fig. 3A). Among them, the Myrtaceae ranked first with 8 species reported for use in diabetes treatment in Indonesia. This was followed by Piperaceae (7 species), Compositae (6 species), and both Asteraceae and Fabaceae (5 species each). The Mornigaceae family, along with 29 other families, ranked lowest with only 1 species each reported for use in treating diabetes. When analyzing the plant parts used in treatment, leaves were the most commonly utilized, accounting for 56%, followed by the use of whole parts (14%), and stems, aerial parts and fruits, each contributing 5% (Fig. 3B).

The included publications were also assessed based on the type of scientific investigation conducted

(Fig. 3C). Of the 108 articles, 40% were based on *in vitro* assessments, followed closely by *in vivo* animal studies (39%). *In silico* computer modeling approaches accounted for 15% of the studies. Additionally, clinical trials made up 6% of the research on medicinal plants used in Indonesia for diabetes treatment.

In silico studies of Indonesian antidiabetic medicinal plants

Computational chemistry has facilitated the virtual screening of interactions between ligands or drug leads and target enzymes. This approach offers a significant advantage by drastically reducing screening time compared to conventional *in vitro* bioassay guided protocols. Moreover, advancements in Artificial intelligence-assisted phytochemical techniques and modern instrumentation have streamlined the



◀ **Fig. 3** Meta analysis of 108 articles covering 109 plant species. A. Species distribution of antidiabetic plants by family. B. Plant parts used and studied for treating diabetes. C. Type of studies involved in antidiabetic studies of Indonesian medicinal plants

isolation and characterisation of secondary metabolites, accelerating the discovery of bioactive molecules from natural products. The increasing availability of secondary metabolite databases from medicinal plants has further enabled targeted computation-based drug screening. Several studies have successfully complemented these *in silico* findings with *in vitro* validation. The 108 articles featured these advancements and screening techniques, as discussed below. In particular, several Indonesian medicinal plants traditionally used for diabetic treatment have been investigated through metabolomics profiling to identify their bioactive constituents. One such study analysed the leaves of *Smallanthus sonchifolius* (Poepp) H. Robinson collected from Lembang, West Java, Indonesia. Metabolomics analysis identified 28 compounds, which were subsequently evaluated for

their α -glucosidase inhibitory activity using molecular docking. The study revealed that several compounds (Fig. 4), nystose **1**, 1-kestose **2**, luteolin-3'-7-di-*O*-glucoside **3**, and 1,3-*O*-dicaffeoilquinic acid **4** isomers exhibited docking score from -100.216 to -115.657 kcal.mol⁻¹. These values were comparable to that of the standard drug acarbose **5**, which had a docking score of -115.774 kcal/mol (Aziz et al. 2021).

Studies on the crude ethyl acetate extract from the fruits of *Terminalia catappa* L. demonstrated inhibitory activity against α -glucosidase with an IC₅₀ value of 192.51 μ g/mL, compared to the positive control, acarbose, which had an IC₅₀ of 17.52 μ g/mL. Phytochemical profiling of the crude extracts using GC-MS led to the identification of thirteen compounds. Further analysis of the GC-MS data, combined with *in silico* approach to identify active phytoconstituents (Fig. 5) revealed β -sitosterol **6**, β -sitosterol acetate **7** and sitostenone **8** as potential antidiabetic agents, with binding energy values of -10.61 , -11.14 , and -9.79 kcal/mol, respectively (Sari et al. 2016).

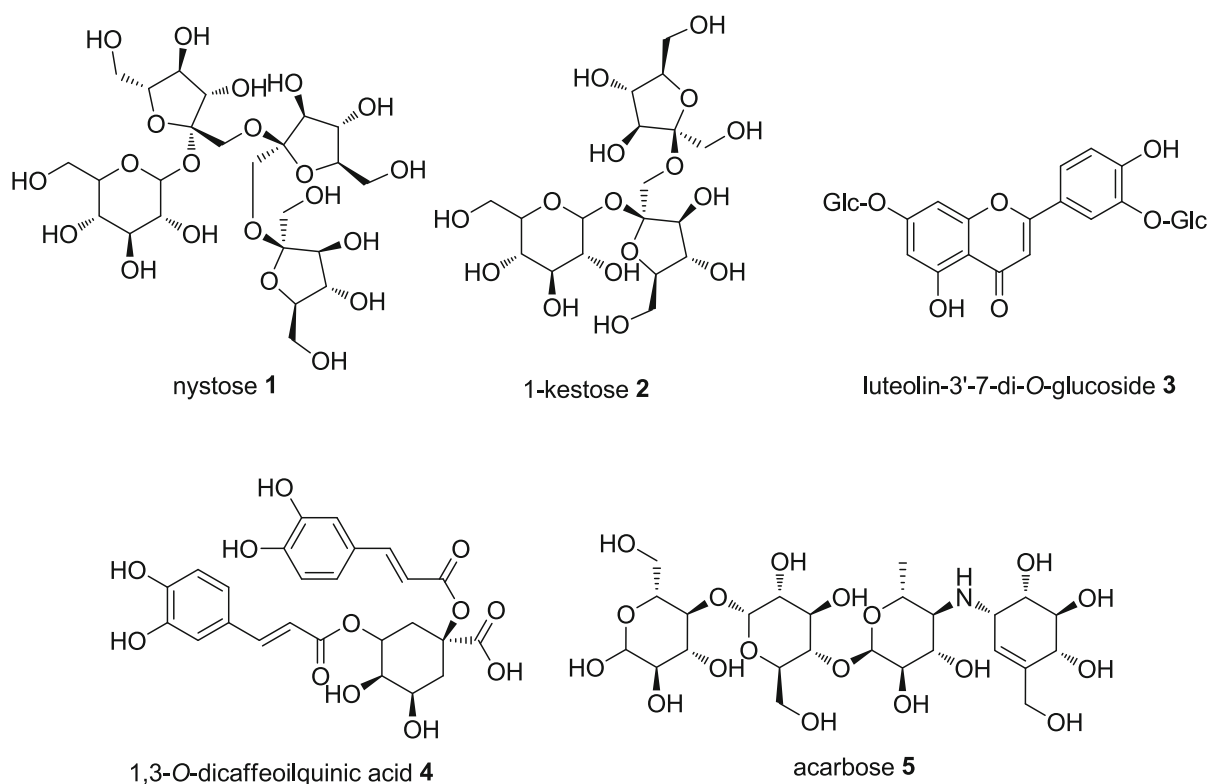


Fig. 4 Antidiabetic compounds **1–4** from *Smallanthus sonchifolius* and the standard drug acarbose **5**

Fig. 5 Antidiabetic compounds **6–8** from *Terminalia catappa*

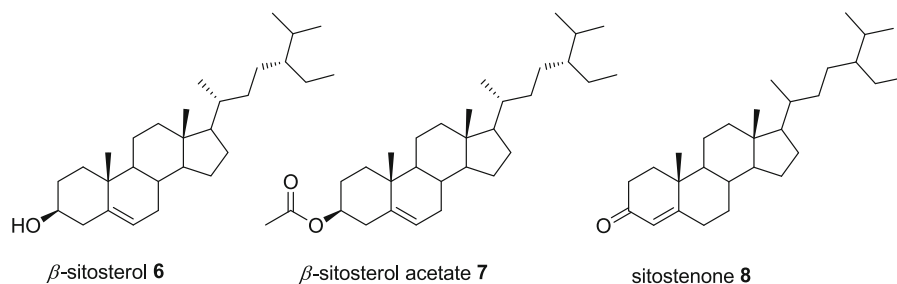
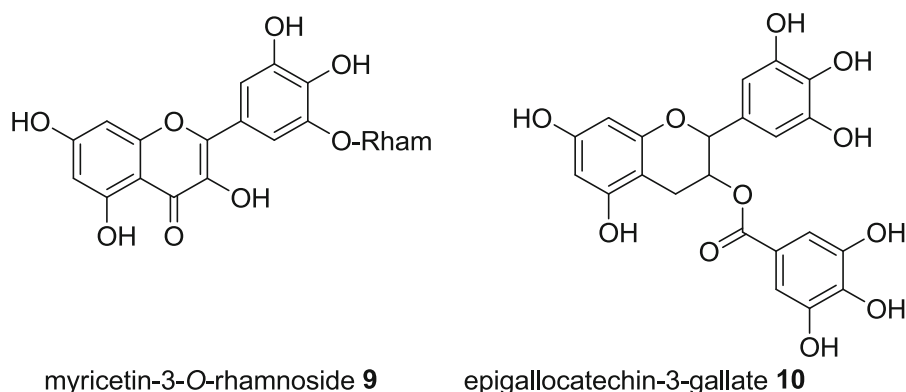


Fig. 6 Antidiabetic compounds **9–10** isolated from *Syzygium polyanthum*



A decoction of the leaves of *Syzygium polyanthum* (Wight) Walp (Myrtaceae) is traditionally prepared by Indigenous communities in Indonesia to help lower blood glucose levels. Metabolomics investigations on leaf samples collected from Bogor, Indonesia, identified fractions responsible for α -glucosidase inhibitory activity. Further spectrometric and spectroscopic analyses of these fractions revealed the presence of myricetin-3-*O*-rhamnoside **9** and epigallocatechin-3-gallate **10** (Fig. 6). Docking experiments showed that both compounds exhibited strong binding affinities to the α -glucosidase active site, with binding energy values of -8.47 and -8.19 kcal/mol, respectively, compared to the positive control acarbose **5**, which had a binding energy value of -10.13 kcal/mol (Syabana et al. 2022).

GC–MS based phytochemical profiling of *Psychotria malayana* Jack leaves obtained from Jambi, Indonesia, successfully identified nine metabolites. Their antidiabetic potential was evaluated through molecular docking experiments targeting α -glucosidase. Among the identified compounds, cholesta-7,9(11)-diene-3-ol **11**, β -tocopherol **12** and stigmast-5-ene **13** exhibited notable binding affinities, with energy values of -6.1, -8.6, -9.4 kcal/mol,

respectively. These results were comparable to those of quercetin **14** and the control ligand ADG, which showed binding energies of -8.4 and -6.0 kcal/mol, respectively (Fig. 7) (Nipun et al. 2021).

Some species of Indonesian medicinal plants used to treat diabetes are also found in other countries. Therefore, in addition to conducting in-house phytochemical studies on samples collected in Indonesia, it is beneficial to document and compare metabolites from the same species collected elsewhere. However, due to differences in habitat and ecological conditions, the chemical composition and biological activities of these plants may vary significantly. While data from other countries can offer valuable scientific insights, it is advisable to study Indonesian medicinal plants locally whenever financial resources permit. For instance, a study of *Imperata cylindrica* (L.) P. Beauv. Collected in Indonesia identified 5-methoxyflavone **15**, 6-hydroxy-5-methoxyflavone **16**, 7-hydroxy-4-methoxy-5-methylcoumarin **17**, and siderin **18** as potential α -glucosidase inhibitors, demonstrating binding activities comparable to the standard miglitol (Fig. 8) (Rohman et al. 2021). Similarly, in silico investigations of constituents from *Solanum torvum* Sw. (Takokak plant) suggested methyl caffeate **19** as a

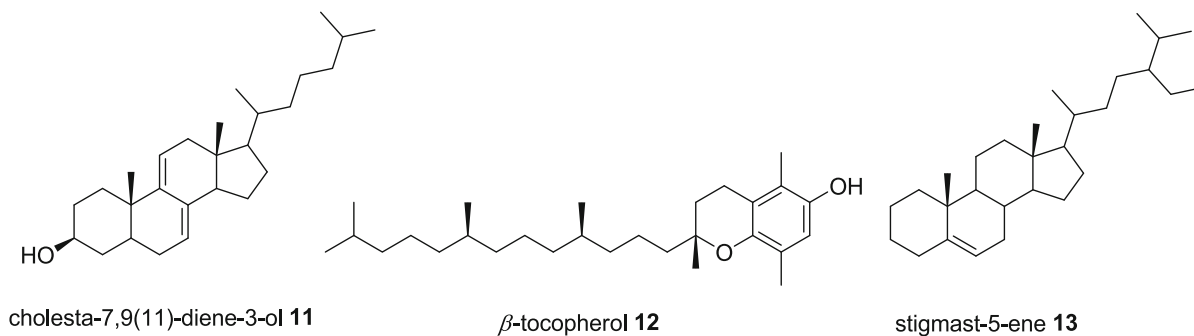
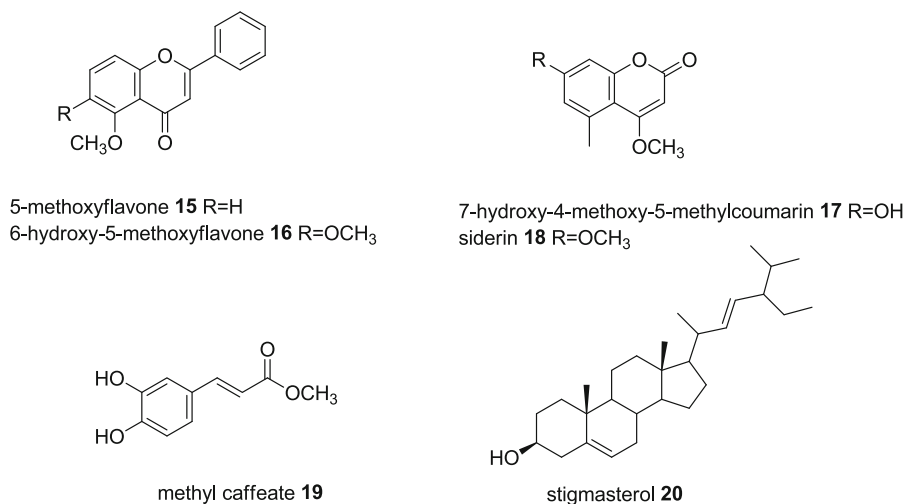


Fig. 7 Antidiabetic compounds **11–13** derived from *Psychotria malayana*

Fig. 8 Antidiabetic compounds derived from *Imperata cylindrica*, *Solanum torvum* and *Morinda citrifolia*



potential antidiabetic marker, with a binding affinity of $-6.8 \text{ kcal}\cdot\text{mol}^{-1}$ against α -glucosidase (Fig. 8) (Putri et al. 2022).

Phytosterol constituents of *Morinda citrifolia* L., specifically stigmasterol **20** and β -sitosterol **6** were also evaluated in silico for their antidiabetic potential. Docking studies were conducted using multiple targets: α -amylase (2QV4), α -glucosidase (5NN8), PPAR- γ (2P4Y), and DPP-IV (4PNZ) (Fig. 8). The results showed that both sterols exhibited stronger binding affinities with α -amylase than the standard ligand/drug acarbose **5** (Lolok et al. 2022).

Another important protein target in antidiabetic research is dipeptidyl peptodase-IV (DPP-IV), which plays a role in increasing incretin levels, thereby contributing to the reduction of blood glucose levels. Secondary metabolites extracted from the fruit, leaves and stems of *Momordica charantia* L. have been reported to exhibit DPP-IV inhibitory activity, which

charantin **21** identified as the most potent, showing a binding energy of -9.8 kcal/mol surpassing that of the native ligand PF2, which had a binding energy of -8.7 kcal/mol (Deviana and Diniatik 2021). Similarly, phytochemicals from *S. sonchifolius*, including 13(*R*)-hydroxyoctadeca-(9*E*,11*E*,15*Z*)-trienoic acid **22**, benzylalcohol 7-*O*- α -L-arabinopyranosyl(1" \rightarrow 2')- β -D-glucopyranoside **23**, 13(*R*)-hydroxyoctadeca-(9*Z*,11*E*,15*Z*)-trienoic acid **24**, were evaluated for DPP-IV inhibitory activity. However, none of these compounds demonstrated a higher binding affinity than the standard inhibitor, sitagliptin (Fig. 9) (Sinurat et al. 2021). The same docking protocol was applied to Ongga (*Strychnos lucida* R.Br.), where ten previously reported phytoconstituents were screened against several antidiabetic targets, including human aldose reductase (2HV5), human maltase-glucoamylase (2QMJ), PPAR-gamma (3TY0), pancreatic beta-cell SUR1 (6PZA), and human DPP-IV (3BJM). While

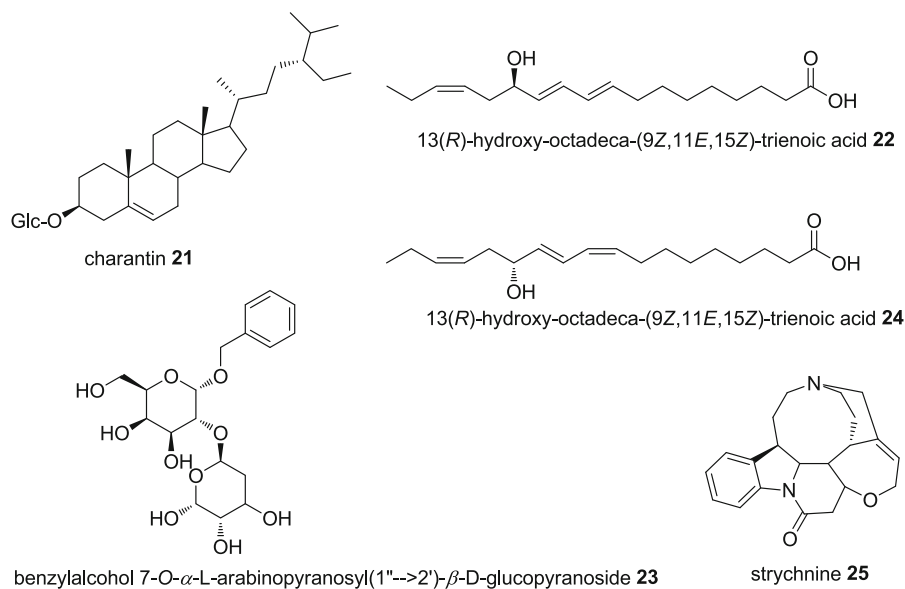


Fig. 9 Antidiabetic compounds originated from *Momordica charantia* and *Strychnos lucida*

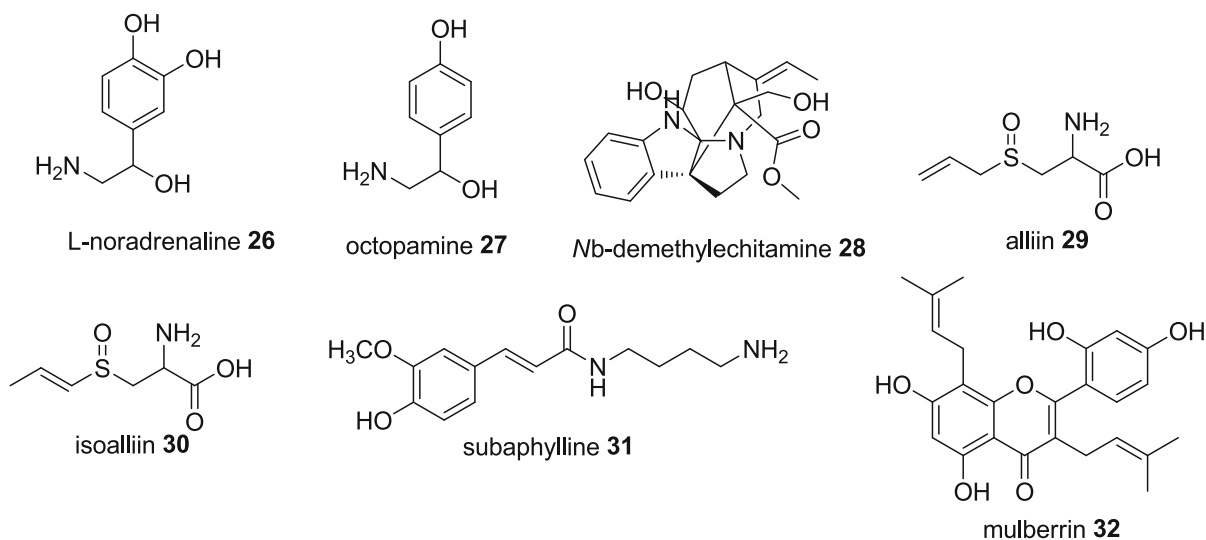


Fig. 10 Antidiabetic compounds identified through structure-based screening of secondary metabolites from the Indonesian Herbal Database

most compounds exhibited lower binding affinities compared to their respective native ligands, strychnine **25** showed notable DPP-IV inhibitory potential with a binding energy of -6.2 kcal/mol, outperforming the standard drug vildagliptin (-5.4 kcal/mol) (Fig. 9) (Setiawansyah et al. 2022).

Studies utilizing the extensive Indonesian medicinal plants database (Indonesian Herbal Database)—

which comprises 1,377 compounds- identified six potential DPP-IV inhibitory agents: L-noradrenaline **26**, octopamine **27**, Nb-demethylechitamine **28**, alliin **29**, isoalliin **30**, and subaphylline **31** (Farkhani et al. 2020; Naeem et al. 2012). In addition, a structure-based pharmacophore virtual screening conducted using compounds from the same database highlighted mulberrin **32** as the most promising candidate for

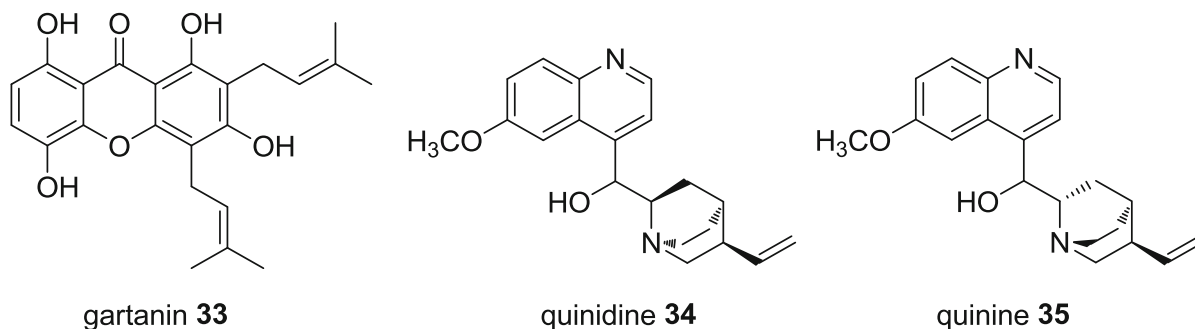


Fig. 11 Secondary metabolites from Indonesian medicinal plants as potential SIRT1 activator candidates

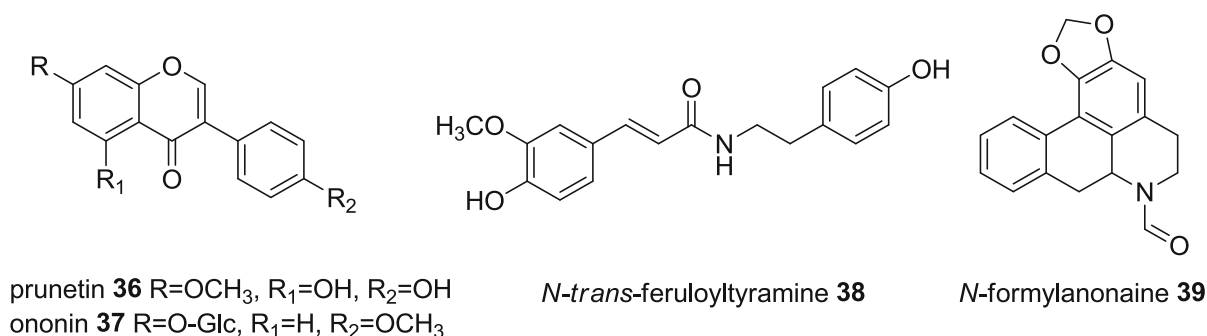


Fig. 12 Phenolic and alkaloid antidiabetic compounds generated through ligand-based in silico virtual screening of secondary metabolites from Indonesian medicinal plants database

SIRT1 activator. This prediction was subsequently validated through an in vitro bioassay, which confirmed its activity with an IC₅₀ value of 2.10 μM (Fig. 10) (Azminah et al. 2019).

In silico ligand-based screening using the Indonesian medicinal plant database, which comprises 1,377 compounds, identified gartanin **33**, quinidine **34**, and quinine **35** as the top candidates for SIRT1 activation (Fig. 11). Furthermore, in vitro experiments confirmed the SIRT1-activating potential of these compounds, demonstrating IC₅₀ values of 2.10, 1.79, 1.71, 1.14 μM, respectively (Azminah et al. 2019).

Compounds from the Indonesian medicinal plant database was also screened for their potential as aldose reductase inhibitors using Random Forest (RF) modelling. This analysis suggested two compounds, prunetin **36** and ononin **37**, as having the highest RF scores. Subsequent in vitro experiments indicated inhibitory activities of 58% and 52%, respectively, at a concentration of 15 μM (Fig. 12) (Naeem et al. 2012).

Beyond molecular docking approaches, computational studies also utilized molecular similarity

assessments with approved drug molecules, i.e. employing the Tanimoto molecular index. One such study evaluated 595 compounds from four commonly used medicinal plants, pare (*Momordica charantia* L.), sembung (*Blumea balsamifera* (L.) DC.), bratawali (*Tinospora crispa* (L.) Hook. f. & Thomson), and jahe (*Zingiber officinale* Roscoe). The results revealed that *T. crispa* derived compounds, *N-trans*-feruloyltyramine **38** and *N*-formylanonaine **39**, exhibited the highest similarity index when compared with 19 FDA-approved antidiabetic agents (Fig. 12) (Bakri et al. 2016).

In vitro studies of Indonesian antidiabetic medicinal plants

To date, several in vitro studies have investigated various Indonesian medicinal plants for their potential anti-hyperglycaemic properties (Table 1). These studies have evaluated 57 plant species from 32 different families, focusing on phytochemicals extracted from

Table 1 In vitro antidiabetic activity of Indonesian medicinal plants

Family	Species	Part	Sample	Object/target	IC ₅₀	Inhibition percentage	Positive control	Ref.
Acanthaceae	<i>Andrographis paniculata</i> (Burm.f.) Wall. ex Nees	Herb	Ethanol extract	DPP-IV		37.03 ± 0.65%	Sitagliptin = 74.77 ± 0.3%	Riyanti et al. (2016)
	<i>Ruellia tuberosa</i> L.	Leaves	Ethanol extract	DPP-IV		30.09 ± 1.30%	Sitagliptin = 74.77 ± 0.3%	Riyanti et al. (2016)
Anisophyllaceae	<i>Anisophyllea disticha</i> Baill	Leaves	Triterpene isolate 1	α-glucosidase	46.246 ± 0.166 µg/mL		Acarbose = 19.737 ± 0.046 µg/mL	Fikriyah et al. (2020)
		Leaves	Triterpene isolate 2	α-glucosidase	80.273 ± 0.080 µg/mL			
		Leaves	Methanol extract	α-glucosidase	47.765 ± 0.127 µg/mL		Acarbose = 18.283 ± 0.375 µg/mL	Almurdani et al. (2020)
Apiaceae	<i>Centella asiatica</i> (L.) Urb	Leaves	Methanol extract	α-amylase		42.3 ± 4.7%		Gunawan-Puteri et al. (2012)
Apocynaceae	<i>Catharanthus roseus</i> (L.) G. Don	Bark	Methanol extract	α-amylase		45.3 ± 2.8%		Gunawan-Puteri et al. (2012)
	<i>Parameria barbata</i> K. Schum	Bark	Methanol extract	α-amylase		17.4 ± 2.8%		Gunawan-Puteri et al. (2012)
Araceae	<i>Areca cathaca</i> Burm.f	Fruit	Methanol extract	α-amylase		92.5 ± 7.9%		Gunawan-Puteri et al. (2012)
Asteraceae	<i>Artemisia vulgaris</i> L.	Leaves	Methanol extract	α-amylase		84.3 ± 2.8%		Gunawan-Puteri et al. (2012)
	<i>Chromolaena odorata</i> (L.) R.M. King & H. Rob	Leaves	Ethyl acetate extract	α-glucosidase	779.54 ± 6.16 µg/mL		Acarbose = 7.67 ± 1.86 µg/mL	Putri and Fatmawati (2019)
			Odoratenin		> 62.5 µg/mL			
			Isosakuranetin		> 312.5 µg/mL			
	<i>Gynura procumbens</i> (Lour.) Merr	Stalk and leaves	Methanol extract	α-amylase		28.2 ± 8.5%		Gunawan-Puteri et al. (2012)
	<i>Pluchea indica</i> (L.) Less	Leaves	3,5-di- <i>O</i> -caffeoylquinic acid	α-glucosidase	1166 µM		Acarbose = 0.5 µM	Arsiningtyas et al. (2014)
			4,5-di- <i>O</i> -caffeoylquinic acid methyl ester		208 µM			
			3,4,5-tri- <i>O</i> -caffeoylquinic acid methyl ester		2 µM			

Table 1 continued

Family	Species	Part	Sample	Object/target	IC ₅₀	Inhibition percentage	Positive control	Ref.
			3,4,5-tri- <i>O</i> -caffeoylquinic acid		13 µM			
			1,3,4,5-tetra- <i>O</i> -caffeoylquinic acid		11 µM			
	<i>Cosmos caudatus</i> Kunth	Leaves	Ethanol extract	α-glucosidase	77.17 ± 37.08 µg/mL		Quercetin = 1.38 ± 0.433 µg/mL	Firdaus et al. (2021)
	<i>Smalantius sonchifolius</i> (Poepp.) H. Rob	Leaves	Ethanol extract	DPP-IV		52.84 ± 2.01%	Stagliptin = 74.77 ± 0.3%	Riyanti et al. (2016)
	<i>Tithonia diversifolia</i> (Hemsl.) A. Gray	Leaves	Ethanol extract	DPP-IV		16.8 ± 1.34%	Stagliptin = 74.77 ± 0.3%	Riyanti et al. (2016)
	<i>Wedelia biflora</i> (L.) DC	Leaves	Methanol extract	α-glucosidase	211.15 µg/mL			Manggallo et al. (2019)
Boraginaceae	<i>Cordia myxa</i> L.	Leaves	Chloroform extract Ethanol extract	α-glucosidase	112.56 µg/mL 35.89 µg/mL		Acarbose = 117.20 µg/mL	Malik and Ahmad (2016)
Combretaceae	<i>Terminalia catappa</i> L.	Fruit	Ethyl acetate extract	α-glucosidase	192.51 µg/mL		Acarbose = 17.52 µg/mL	Sari et al. (2016)
Convolvulaceae	<i>Merremia mammosa</i> (Lour.) Hallier f	Rhizome	Ethanol extract	DPP-IV		17.12 ± 1.95%	Stagliptin = 74.77 ± 0.3%	Riyanti et al. (2016)
		Leaves	<i>n</i> -hexane extract	α-glucosidase		66.19 ± 0.41%	Acarbose = 54.85 ± 1.48%	Ratnadewi et al. (2020)
Costaceae	<i>Costus speciosus</i> (J.Koenig) Sm	Leaves	Ethanol extract	DPP-IV		25.92 ± 21.60%	Stagliptin = 74.77 ± 0.3%	Riyanti et al. (2016)
Cucurbitaceae	<i>Momordica charantia</i> Descourt	Semen	Ethanol extract	DPP-IV		41.66 ± 1.63%	Stagliptin = 74.77 ± 0.3%	Riyanti et al. (2016)
Cymodoceaceae Vines	<i>Cymodocea rotundata</i> Asch. & Schweinf	All parts	Ethanol extract	α-glucosidase	429.28 ± 8.89 µg/mL		Acarbose = 197 ± 3.07 µg/mL	Widiyanto et al. (2018)
Euphorbiaceae	<i>Antidesma bunius</i> (L.) Spreng	Leaves	Ethyl acetate extract	α-amylase α-glucosidase	α-amylase: 95.39 ± 4.27% α-glucosidase: 93.17 ± 4.95%		Acarbose-α-amylase: 91.06 ± 2.15% α-glucosidase: 54.85 ± 1.48%	Ratnadewi et al. (2020)
	<i>Antidesma montanum</i> Blume	Leaves	Ethyl acetate extract, <i>n</i> -hexane extract	α-amylase α-glucosidase	α-amylase: 46.45 ± 4.03% α-glucosidase: 79.84 ± 3.46%		Acarbose-α-amylase: 91.06 ± 2.15% α-glucosidase: 54.85 ± 1.48%	Ratnadewi et al. (2020)
	<i>Euphorbia cotinifolia</i> L.	Leaves	Ethanol extract	DPP-IV		23.61 ± 3.27%	Stagliptin = 74.77 ± 0.3%	Riyanti et al. (2016)

Table 1 continued

Family	Species	Part	Sample	Object/target	IC ₅₀	Inhibition percentage	Positive control	Ref.			
Fabaceae	<i>Euphorbia hirta</i> L.	Herb	Ethanol extract	DPP-IV		33.52 ± 0%	Sitagliptin = 74.77 ± 0.3%	Riyanti et al. (2016)			
	<i>Macaranga tanarius</i> Müll.Arg	Leaves	Methanol extract	α-amylase		18.6 ± 1.4%		Gunawan-Puteri et al. (2012)			
	<i>Phyllanthus urinaria</i> L.	Stalk and leaves	Aqueous methanol extract	α-amylase		98.0 ± 5.8%		Gunawan-Puteri et al. (2012)			
Fabaceae	<i>Abrus precatorius</i> L.	Leaves	Galic acid	Porcine pancreatic α-amylase	31 μM	23%		Yonemoto et al. (2014)			
			Corilagin			21%					
			Macatamin B			33%					
Hydrocharitaceae	<i>Perocarpus indicus</i> Willd	Leaves	Luteolin Extract	DPP-IV	3.1 mM 71%	25.0 ± 27.16%	Sitagliptin = 74.77 ± 0.3%	Riyanti et al. (2016)			
			Ethanol extract						α-glucosidase	168.15 ± 2.71 μg/mL	Acarbose = 197 ± 3.07 μg/mL
			Ethanol extract								
<i>Thalassia hemprichii</i> (Ehrenb.) Asch	All parts	Ethanol extract	α-amylase	50.4 ± 2.4%	Nurdin and Sukohar (2017)						
						<i>Cinnamomum cassia</i> (L.) D.Don	Fruits	Methanol extract	α-glucosidase	20%	
											<i>Cinnamomum burmannii</i> (Nees & T.Nees) Blume
<i>Pearsea americana</i> Mill	Semen	Ethanol extract	DPP-IV	71.29 ± 0.33%							
					<i>Trigonella foenum graecum</i> L.	Semen	Ethanol extract	DPP-IV	Sitagliptin = 74.77 ± 0.3%		
										<i>Lagerstroemia speciosa</i> (L.) Pers	Leaves
<i>Lagerstroemia loudonii</i> Teijsm. & Binn	Leaves	Ethanol extract	DPP-IV	60.22 ± 2.01%							
					Sitagliptin = 74.77 ± 0.3%	Riyanti et al. (2016)					

Table 1 continued

Family	Species	Part	Sample	Object/target	IC ₅₀	Inhibition percentage	Positive control	Ref.
Meliaceae	<i>Punica granatum</i> L.	Rind	Ethanol extract	DPP-IV		58.79 ± 2.23%	Sitagliptin = 74.77 ± 0.3%	Riyanti et al. (2016)
		Fruit peels	Methanol extract	α -amylase		35.4 ± 0.8%		Gunawan-Puteri et al. (2012)
	<i>Azadirachta indica</i> A. Juss	Leaves	Ethanol extract	DPP-IV		17.78 ± 1.02%	Sitagliptin = 74.77 ± 0.3%	Riyanti et al. (2016)
Menispermaceae			Methanol extract	α -amylase		3.5 ± 2.8%		Gunawan-Puteri et al. (2012)
	<i>Swietenia mahagoni</i> (L.) Jacq	Semen	Ethanol extract	DPP-IV		38.88 ± 22.25%	Sitagliptin = 74.77 ± 0.3%	Riyanti et al. (2016)
	<i>Arcangelisia flava</i> (L.) Merr	Leaves	Ethyl acetate extract, methanol extract	α -amylase α -glucosidase	α -amylase: 64.24 ± 3.53% α -glucosidase: 95.04 ± 3.55%		Acarbose α -amylase: 91.06 ± 2.15% α -glucosidase: 54.85 ± 1.48%	Ratnadewi et al. (2020)
Moraceae	<i>Tinospora crispa</i> Miers	Stem	Ethanol extract	DPP-IV		65.86 ± 1.02%	Sitagliptin = 74.77 ± 0.3%	Riyanti et al. (2016)
		Bark	Methanol extract	α -amylase		16.1 ± 0.3%		Gunawan-Puteri et al. (2012)
	<i>Artocarpus heterophyllus</i> Lam	Leaves	Ethanol extract	DPP-IV		30.55 ± 4.90%	Sitagliptin = 74.77 ± 0.3%	Riyanti et al. (2016)
Myrtaceae	<i>Ficus religiosa</i> L.	Leaves	Ethanol extract	DPP-IV		68.98 ± 1.95%	Sitagliptin = 74.77 ± 0.3%	Riyanti et al. (2016)
	<i>Syzygium aromaticum</i> (L.) Merr. & L.M.Perry	Flower	Methanol extract	α -amylase		16.1 ± 0.3%		Gunawan-Puteri et al. (2012)
	<i>Syzygium polyanthum</i> (Wight) Walp	Leaves	Ethanol extract	<i>p</i> -nitrophenyl- α -D-glucopyranoside		97.37%		Dewijanti et al. (2019)
Piperaceae		Leaves	Acetone water fraction	α -glucosidase	24.8 μ g/mL	97.34%	Acarbose = 0.38 μ g/ml	Syabana et al. (2022)
	<i>Piper betle</i> L.	Leaves	Ethanol extract	α -amylase		71.9% in 5 mg/mL concentration		Chaithan et al. (2020)
	<i>Piper crocatum</i> Ruiz & Pav	Leaves	Ethanol extract	α -glucosidase		1.29%—40.80%	Acarbose = 80.97%	Muhammad et al. (2020)
Plantaginaceae	<i>Plantago major</i> L.	Roots	Methanol extract	α -amylase		67.6 ± 6.6%		Gunawan-Puteri et al. (2012)

Table 1 continued

Family	Species	Part	Sample	Object/target	IC ₅₀	Inhibition percentage	Positive control	Ref.
Rutaceae	<i>Linasia amara</i> Blanco	Leaves	Methanol extract	α -amylase α -glucosidase	α -amylase: 90.49 \pm 2.95% α -glucosidase: 83.33 \pm 3.20%		Acarbose α -amylase: 91.06 \pm 2.15% α -glucosidase: 54.85 \pm 1.48%	Ratnadewi et al. (2020)
Simaroubaceae	<i>Brucea javanica</i> (L.) Merr	Fruits	Methanol extract	α -amylase		7.3 \pm 0.39%		Gunawan-Puteri et al. (2012)
Solanaceae	<i>Physalis angulata</i> L.	Leaves	Ethanol extract	DPP-IV		13.94 \pm 4.08%	Sitagliptin = 74.77 \pm 0.3%	Riyanti et al. (2016)
Thymelaeaceae	<i>Phaleria macrocarpa</i> Boerl	Fruit peels	Ethanol extract	α -glucosidase	1.60 \pm 0.04 mg/L		Acarbose = 1.33 \pm 0.03 mg/L	Irawan et al. (2022)
Verbenaceae	<i>Lantana camara</i> L.	Aerial parts	24-Hydroxylantadene B	Protein tyrosine phosphatase 1B (PTP1B)	7.3 μ M		Oleanolic acid = 1.3 μ M	Abdul et al. (2017)
			24-Hydroxylantadene D		> 18 μ M			
			24-Hydroxylantadene X		> 18 μ M			
			22-Hydroxy-4-epi-hederagonic acid		> 21 μ M			
			3 β -Hydroxylantadene C		7.3 μ M			
			Icterogenin		11 μ M			
			4- <i>epi</i> -Hederagonic acid		8.1 μ M			
			Oleanolic acid		2 μ M			
			22 β -Oleanolic acid		7.9 μ M			
			3 β -Hydroxylantadene A		7.2 μ M			
			3 β -Hydroxy lantadene B		5.1 μ M			
			22-Hydroxyoleanonic acid		6.9 μ M			
			Lantadene B		5.5 μ M			
			Lantadene A		5.2 μ M			
			Oleanonic acid		6.9 μ M			
			Lantadene D		7.9 μ M			
			Pomonic acid		10.5 μ M			
			Pomolic acid		10.6 μ M			
			Lantamalic acid		7.5 μ M			
					5.1 μ M			

Table 1 continued

Family	Species	Part	Sample	Object/target	IC ₅₀	Inhibition percentage	Positive control	Ref.
			Cameric acid		> 16 μM			
			Pectolinarin		> 33 μM			
			Lantanolic acid		7.3 μM			
			22β-Tigloyloxylantanolic acid		> 16 μM			
			Hispidulin		> 33 μM	36% inhibition at 32 μM		
			Pectolinarigenin			Single extract = 2.930 mg/dL		
Zingiberaceae		<i>Curcuma longa</i> L.	Rhizome	Aqueous extract	α-glucosidase			
		<i>Zingiber officinale</i> Roscoe	Rhizome	Aqueous extract	α-glucosidase		< 25%	

leaves, fruits, seeds, barks, fruit peels, aerial parts, rhizomes, roots, stalks, and flowers. Most samples were prepared as crude extracts, and antidiabetic activity was assessed using enzymatic assays targeting α-glucosidase, α-amylase, dipeptidyl peptidase-IV (DPP-IV), *p*-nitrophenyl-α-D-glucopyranoside, protein tyrosine phosphatase 1B, and porcine pancreatic α-amylase. The results of these in vitro experiments were reported as IC₅₀ values and/or percentage inhibition. Among the tested species, those belonging to eleven plant families, including Asteraceae, Boraginaceae, Convolvulaceae, Euphorbiaceae, Hydrocharitaceae, Lythraceae, Menispermaceae, Myrtaceae, Rutaceae, Thymelaeaceae, and Verbenaceae demonstrated varying degrees of antidiabetic activity.

Asteraceae

The in vitro evaluation of the Asteraceae family focused on several species, including *Smilax sonchifolius* (Poepp.) H. Rob., *Tithonia diversifolia* (Hemsl.) A. Gray., *Artemisia vulgaris* L., and *Gynura procumbens* (Lour.) Merr., *Chromolaena odorata* (L.) R. M. King & H. Rob., and *Wedelia biflora* (L.) DC. These species exhibited moderate to low activity against glucose metabolism-related enzymes, with IC₅₀ values ranging from 62.5 to 779.5 μg/mL and inhibition percentages ranging from 16.8 ± 1.34 to 84.3 ± 2.8% (Gunawan-Puteri et al. 2012; Mangallo et al. 2019; Putri and Fatmawati 2019; Riyanti et al. 2016). A phytochemical investigation of *Pluchea indica* (L.) Less. led to the isolation several caffeoylquinic acid derivatives: 3,5-di-*O*-caffeoylquinic acid **40**, 4,5-di-*O*-caffeoylquinic acid methyl ester **41**, 3,4,5-tri-*O*-caffeoylquinic acid methyl ester **42**, 3,4,5-tri-*O*-caffeoylquinic acid **43**, and 1,3,4,5-tetra-*O*-caffeoylquinic acid **44** (Fig. 13) (Arsiningtyas et al. 2014). Interestingly, compounds **42**, **43** and **44** demonstrated strong α-glucosidase inhibitory activity, with IC₅₀ values of 2, 11 and 13 μM, respectively, compared to acarbose as the positive control (IC₅₀ = 0.5 μM). In contrast, compounds **40** and **41** were significantly less active, with IC₅₀ values of 208 and 1166 μM, respectively (Arsiningtyas et al. 2014). Previous studies discovered that the methyl esterification of the quinic acid moiety enhance α-glucosidase inhibitory activity, and the number of caffeoyl groups contributes significantly to the compound's

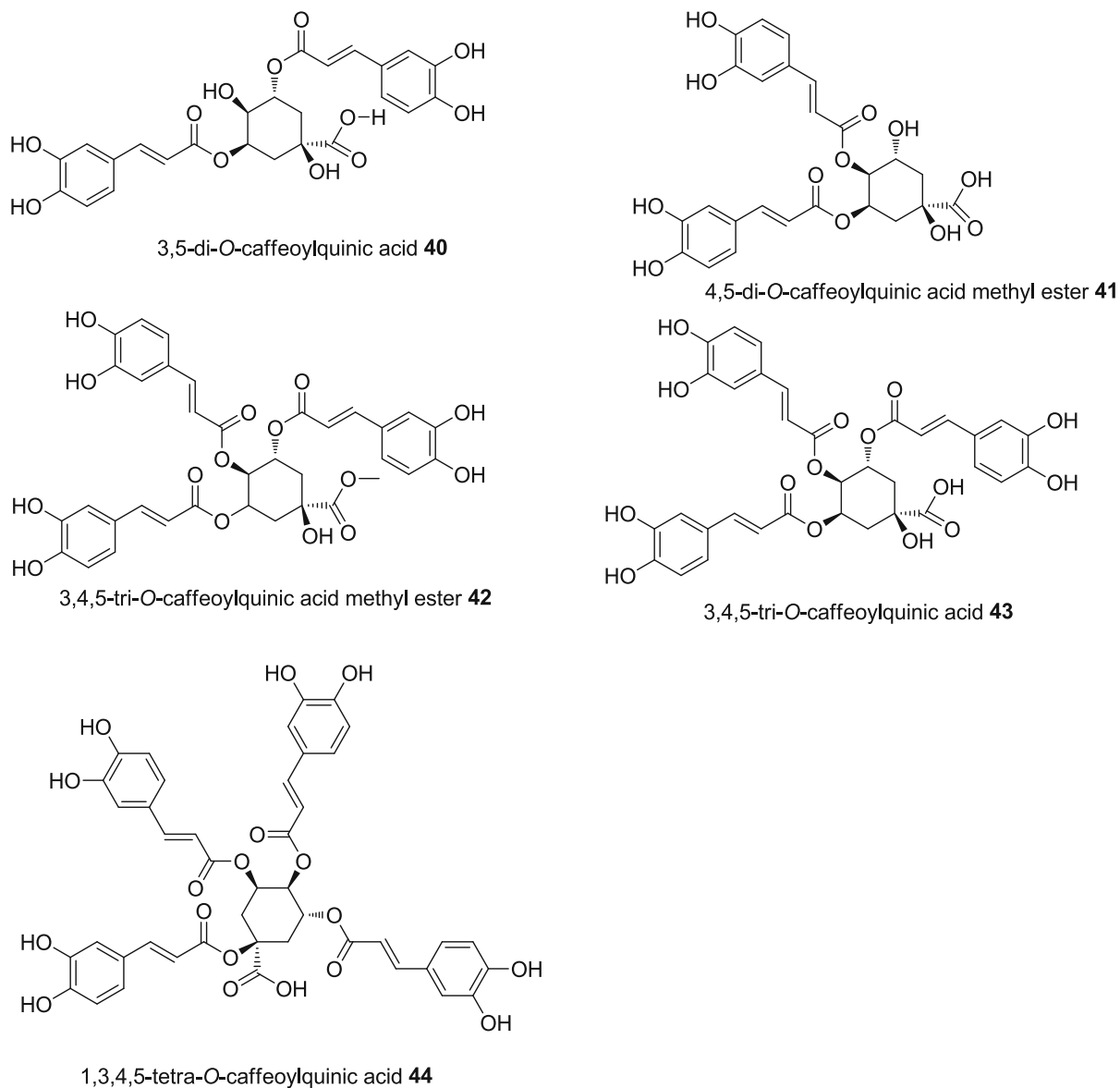


Fig. 13 Caffeoylquinic acid derivatives from Indonesian *Pluchea indica* with antidiabetic potential

enzyme inhibition potential (Arsiningtyas et al. 2014). Therefore, caffeoylquinic acid derivatives from *P. indica* may hold promise as therapeutic agents for the management of postprandial hyperglycaemia.

Boraginaceae

An in vitro study on the Boraginaceae species, *Cordia myxa* L. showed that its ethanol extract exhibited higher α -glucosidase inhibitory activity than the positive control, acarbose with IC₅₀ values of 35.89

and 117.20 μ g/mL, respectively (Malik and Ahmad 2016).

Convolvulaceae

The medicinal plant *Merremia mammosa* (Lour.) Hallier f., which belongs to the Convolvulaceae family, has been reported to possess antidiabetic properties (Ratnadewi et al. 2020). The *n*-hexane extract obtained from *M. mammosa* leaves demonstrated moderate inhibitory activity, reaching up to

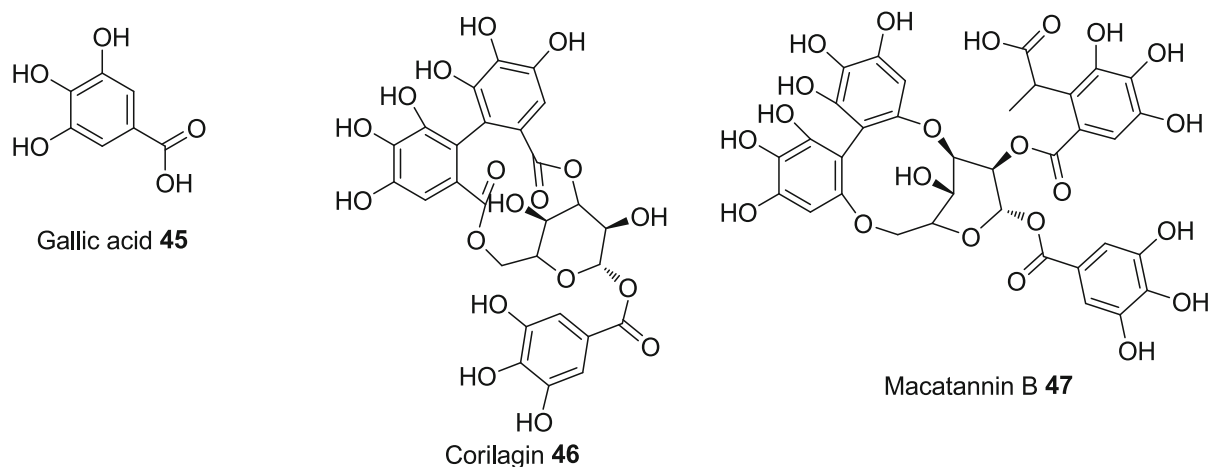


Fig. 14 Gallic acids derivatives with antidiabetic activities from *Phyllanthus urinaria* herbs

66.19 ± 0.41% at a concentration of 25 µgGAE/mL. Notably, the inhibitory effect was considerably significant compared to the positive control, acarbose, which showed 54.85 ± 1.48% inhibition (Ratnadewi et al. 2020).

Euphorbiaceae

A study conducted on *Euphorbia cotinifolia* L. and *Euphorbia hirta* L., both belonging to the Euphorbiaceae family, demonstrated weak α -glucosidase inhibitory activity, with respective inhibition values of 23.61 ± 3.27 and 33.52 ± 0%. These results were considerably lower compared to the standard positive control drug, sitagliptin, which exhibited 74.77 ± 0.3% inhibition at a concentration of 2.5 µg/mL (Riyanti et al. 2016). Similarly, the crude extract of *Macaranga tanarius* Müll.Arg. failed to significantly impede the DPP-IV enzyme, showing an inhibition level of 18.6 ± 1.4% at a concentration of 5 mg/mL (Gunawan-Puteri et al. 2012). In contrast, the ethyl acetate extract of *Antidesma bunius* (L.) Spreng. leaves demonstrated strong hypoglycemic activity, with α -glucosidase and α -amylase inhibition values of 93.17 ± 4.95 and 95.39 ± 4.27%, respectively, at a concentration of 25 µgGAE/mL (Ratnadewi et al. 2020). A significant decrement in α -glucosidase activity was also reported in an in vitro study on *Antidesma montanum* Blume., where the *n*-hexane leaf extract showed 79.84 ± 3.46% inhibition at the same concentration (Ratnadewi et al. 2020). These findings indicate that at a concentration of 25

µgGAE/mL, *A. bunius* and *A. montanum* extracts exhibit more pronounced enzyme inhibitory effects compared to acarbose, which showed 54.85 ± 1.48% inhibition against α -glucosidase and 91.06 ± 2.15% against α -amylase (Ratnadewi et al. 2020). Furthermore, previous investigations revealed the antidiabetic potential of the aqueous methanol extract of *Phyllanthus urinaria* L. against porcine pancreatic amylase (PPA), along with three isolated compounds namely gallic acid **45**, corilagin **46**, and macatannin B **47** (Fig. 14) (Gunawan-Puteri et al. 2012). These compounds showed PPA inhibitory activity values of 98.0, 23, 21, and 33%, respectively, at a concentration of 5 mg/mL. However, despite their promising antidiabetic activity, the absence of a standard positive control drug limits the ability to fully assess and compare their effectiveness.

Hydrocharitaceae

Among the species in the Hydrocharitaceae family, *Enhalus acoroides* (L.f.) Royle. was examined for its antidiabetic potential and demonstrated α -glucosidase inhibitory activity with an IC₅₀ value of 168.15 ± 2.71 µg/mL. The ethanolic extract of *E. acoroides* showed significant activity comparable to that of the positive control, acarbose (IC₅₀ = 197 ± 3.07 µg/mL) (Widiyanto et al. 2018). In comparison, the α -glucosidase inhibition assay of *Thalassia hemprichii* (Ehrenb.) Asch. ethanol extract displayed weaker activity, with an IC₅₀ value of

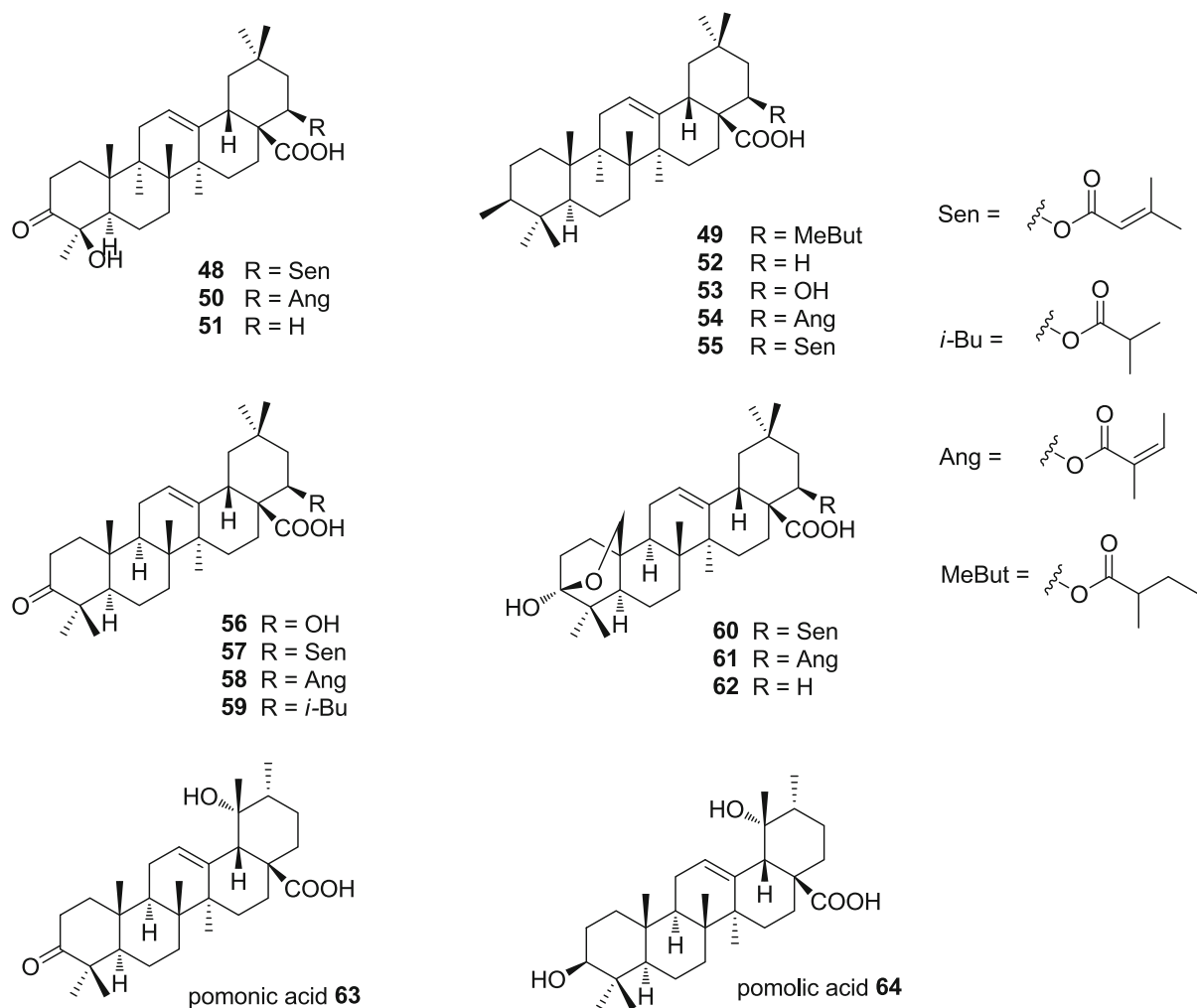


Fig. 15 Bioactive compounds from medicinal plants of the Verbenaceae family with the potential to modulate carbohydrate metabolism

$425.86 \pm 5.15 \mu\text{g/mL}$ compared to acarbose ($\text{IC}_{50} = 197 \pm 3.07 \mu\text{g/mL}$) (Widiyanto et al. 2018).

($74.77 \pm 0.3\%$), with values of 60.22 ± 2.01 and $58.79 \pm 2.23\%$, respectively (Riyanti et al. 2016).

Lhytraceae

From the three species in the Lhytraceae family, only the methanol extract of *Lagerstroemia speciosa* (L.) Pers. leaves showed notable α -glucosidase inhibition, achieving $83.33 \pm 3.20\%$, surpassing that of the positive control, acarbose ($54.85 \pm 1.48\%$) (Ratnadewi et al. 2020). Contrarily, crude extracts of *Lagerstroemia loudonii* Teijsm. & Binn., and *Punica granatum* L. displayed lower DPP-IV inhibitory activity than the standard drug sitagliptin

Menispermaceae

Tinospora crispa Miers., a member of Menispermaceae family, has been traditionally use in diabetic treatment. However, in vitro evaluation of its 96% ethanolic stem extract revealed only modest DPP-IV inhibitory activity ($65.86 \pm 1.02\%$) at a concentration of $2.5 \mu\text{g/mL}$, which was lower than that of sitagliptin ($74.77 \pm 0.3\%$) (Riyanti et al. 2016). Conversely, bioassay-guided screening of *Arcangelisia flava* (L.) Merr., a well-known medicinal plant, revealed strong α -glucosidase inhibitory activity. Its methanol leaf

extract displayed $94.44 \pm 0.43\%$ inhibition at 25 $\mu\text{gGAE/mL}$, comparable to acarbose ($54.85 \pm 1.48\%$) (Ratnadewi et al. 2020). Nevertheless, no further phytochemical studies were performed to isolate its bioactive constituents.

Myrtaceae

Prior investigations have reported the antidiabetic activity of two Indonesian medicinal plants from the Myrtaceae family, namely *Syzygium polyanthum* (Wight) Walp. and *Syzygium aromaticum* (L.) Merr. & L.M.Perry. The ethanol extract of *S. polyanthum* leaves exhibited strong enzymatic hydrolysis inhibition of *p*-nitrophenyl- α -D-glucopyranoside (97.37%), though no standard control was used (Dewijanti et al. 2019). In another study of the acetone water extract from the same species showed α -glucosidase inhibitory activity with an IC_{50} of 24.8 $\mu\text{g/mL}$, which was subordinate to its positive control, acarbose ($\text{IC}_{50} = 0.38 \mu\text{g/mL}$) (Syabana et al. 2022). *S. aromaticum*, commonly known as ‘*cengkeh*’, is a tropical evergreen plant with typical aromatic flower buds. The methanol flower extract exhibited poor α -amylase inhibition ($35.4 \pm 0.8\%$) at a concentration of 5 mg/mL (Gunawan-Puteri et al. 2012).

Rutaceae,

Lunasia amara Blanco, a sparsely branched shrub and the only investigated Indonesian species in the Rutaceae family, has shown promising hypoglycemic activity. Its methanol leaves extract inhibited α -glucosidase by $83.33 \pm 3.20\%$ at 25 $\mu\text{gGAE/mL}$, exceeding the inhibition of acarbose ($54.85 \pm 1.48\%$) (Ratnadewi et al. 2020). However, the antidiabetic bioactive constituents have not yet been explored.

Thymelaceae

Phaleria macrocarpa Boerl., locally known as ‘*mahkota dewa*’, is a famous Indonesian native medicinal plant belonging to the Thymelaceae family. The local people usually use the fruits and leaves to treat several diseases including diabetes mellitus (Ali et al. 2012). An in vitro evaluation of *P. macrocarpa* fruit peels ethanolic extract showed its significant α -glucosidase inhibitory activity with an IC_{50} value of $1.60 \pm 0.04 \text{ mg/L}$ which is notably more potent than

acarbose ($\text{IC}_{50} = 55.84 \text{ mg/L}$) (Irawan et al. 2022). Nevertheless, no further bioprospecting was conducted to obtain the biomarker compounds.

Verbenaceae

In the Verbenaceae family, phytochemical investigation of *Lantana camara* L. aerial part led to the isolation of oleanane triterpenes along with several known flavones (Abdul et al. 2017). Twenty-five compounds were examined for inhibitory activity against protein tyrosine phosphatase 1B (PTP1B), an enzyme which regulates insulin and leptin signalling. Seventeen potential PTP1B inhibitors (Fig. 8), in comparison to standard oleanolic acid ($\text{IC}_{50} = 1.3 \mu\text{M}$), were highlighted including 24-hydroxylantadene B **48** ($\text{IC}_{50} = 7.3 \mu\text{M}$), 3 β -hydroxyantadene C **49** ($\text{IC}_{50} = 7.3 \mu\text{M}$), icterogenin **50** ($\text{IC}_{50} = 11 \mu\text{M}$), 4-epi-hederagonic acid **51** ($\text{IC}_{50} = 8.1 \mu\text{M}$), oleanolic acid **52** ($\text{IC}_{50} = 2 \mu\text{M}$), 22 β -oleanolic acid **53** ($\text{IC}_{50} = 7.9 \mu\text{M}$), 3 β -hydroxylantadene A **54** ($\text{IC}_{50} = 7.2 \mu\text{M}$), 3 β -hydroxylantadene B **55** ($\text{IC}_{50} = 5.1 \mu\text{M}$), 22-hydroxyoleanonic acid **56** ($\text{IC}_{50} = 6.9 \mu\text{M}$), lantadene B **57** ($\text{IC}_{50} = 5.5 \mu\text{M}$), lantadene A **58** ($\text{IC}_{50} = 5.2 \mu\text{M}$), lantadene D **59** ($\text{IC}_{50} = 7.9 \mu\text{M}$), pomonic acid **63** ($\text{IC}_{50} = 10.5 \mu\text{M}$), pomolic acid **64** ($\text{IC}_{50} = 10.6 \mu\text{M}$), lantanilic acid **60** ($\text{IC}_{50} = 7.5 \mu\text{M}$), camaric acid **61** ($\text{IC}_{50} = 5.1 \mu\text{M}$), lantanolic acid **62** ($\text{IC}_{50} = 13 \mu\text{M}$) (Fig. 15) (Abdul et al. 2017). While the remaining compounds exhibited moderate to low inhibitory activity with IC_{50} values ranging from 16 to 33 μM . Compounds **51**, **52**, and **62** demonstrated that oxidation at C-3, hydroxylation at C-24, and an ether linkage between C-3 and C-25 were unfavourable for PTP1B inhibition. These findings are consistent with earlier studies reporting that *L. camara* ameliorated HbA1c levels and body weight profiles. (Venkatachalam et al. 2011).

In vivo studies on Indonesian antidiabetic medicinal plants

In vivo testing is an important step in preclinical drug discovery, offering comprehensive insights into how drug leads interact with the dynamic and complex systems of living organisms (Hefti 2008). These models are also instrumental in predicting human responses to novel treatments (Ioannidis 2012). To

Table 2 In vivo antidiabetic studies on Indonesian medicinal plants

Family	Species	Part of plant	Extract type	Experimental Animal	Induction of diabetes	Standard drug	Dose	Effective dose	Reduction	Time	Ref.
Acanthaceae	<i>Andropogonis paniculata</i> (Burm.f.) Wall. ex Nees	Leaves	Ethanol extract	Mice	Streptozotocin	Metformin 45 mg/kg				21 days	Mardiansyah (2020)
Acoraceae	<i>Acorus calamus</i> L	Radix/roots	Ethyl acetate fraction	C57BL/Ks db/db mice	-	10 mg/kg rosiglitazone	100 mg/kgBW ACE	100 mg/kgBW	ROS 70.1%, ACE 54.5% of serum glucose	21 days	Wu et al. (2009)
Alliaceae	<i>Allium chinense</i> G.Don	Bulbs	Ethanol extract	<i>Rattus norvegicus</i> L	alloxan	Metformin 45 mg/kg BW	250, 500, 750 mg/kgBW	500 mg/kgBW	Liver histopathology	14 days	Rahmah et al. (2021)
Alliaceae	<i>Allium sativum</i> L	Bulbs	Ethanol extract	Wistar rats	Alloxan	Novomix Insulin analog 0.7 U/kgBW	3, 6, and 12 mg/200 gBW	Not significant	Not significant	1 day	Cahya et al. (2015)
Anacardiaceae	<i>Mangifera indica</i> L	Leaves	Ethanol extract	Male mice (Mus musculus)	Alloxan	Glibenclamide	18,375 and 36,75 mg/30 gBW	36,75 mg/30 gBW	54.21% dose 36.75 Glibenclamide 63.06%	14 days	Emelda et al. (2015)
Annonaceae	<i>Annona muricata</i> L	Peels	Ethanol extract	<i>Rattus norvegicus</i> L	Alloxan	Metformin 9 mg/kg BB	50, 75 and 150 mg/kgBW	150 mg/kgBW	25.33% (metformin) 29.33% (150 mg/kg)	10 days	Sarbunan et al. (2021)
Apiaceae	<i>Centella asiatica</i> (L.) Urb	Leaves	Ethanol extract	Zebrafish <i>Danio rerio</i>	Alloxan	Mnformin 25 mg/2 L	100 and 200 mg/2 L Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) Pegagan leaf extract (PLE)	100 mg/kgBW 4 folds	65.50% (metformin) 69.90% (100) 72.20% (200)	12 h	Hayati et al. (2021b)
Asteraceae	<i>Enhydra fluctuans</i>	Aerial	Ethanol extract	Male wistar albino rats	Alloxan	Glibenclamide 0.45 mg/kg	250, 500, and 1000 mg/kgBW	500	29.39 ± 6.72% (500) 35.15 ± 8.13% (gliben)	3 h	Delifta et al. (2020)
	<i>Gynura procumbens</i> (Lour.) Merr	Leaves	Water extract	Male Sprague-Dawley (SD) rats	Streptozotocin	Metformin 500 mg/kg	500 or 1,000 mg/kgBW	1000	29% (1000) and 49% (metformin)	14 days	Hassan et al. (2010)
	<i>Tithonia diversifolia</i> (Hemsl.) A.Gray	Leaves	Ethanol extract (70%)	Sprague dawley rats	Alloxan	Metformin	200, 400, and 600 mg/kgBW	600	81.87 ± 4.38 (600) 75.99 ± 9.67 (metformin)	16 days	Yazid et al. (2021b)

Table 2 continued

Family	Species	Part of plant	Extract type	Experimental Animal	Induction of diabetes	Standard drug	Dose	Effective dose	Reduction	Time	Ref.
Menispermaceae, Caricaceae & Poaceae	Brotowali (<i>Tinospora crispa</i> (L.) Hook. f. & Thomson) and	All parts, Leaves and stem	Water juice	mice (<i>Mus musculus</i>)	Alloxan	Insulin analog	250 and 500 mg / kgBW	500	16% (insulin analog) 15% (500)	5 days	Purnamasari and Rusdianto (2021)
	Papaya (<i>Carica papaya</i> L.) and										
	Sugar cane (<i>Saccharum officinarum</i> L.) as mixture (EBPT)										
Cucurbitaceae	<i>Sechium edule</i> Sw	Fruit	Ethanol extract, ethyl acetate fraction	Albino rats	Streptozotocin and nicotinamide	Metformin 40.5 mg/kg	ethanol extract 45, 100, 150 mg/kgBW	ethyl acetate fraction 100 mg/kg	ethyl acetate fraction 100 metformin 60%	28 days	Siahhaan et al. (2021)
Fabaceae	<i>Glycine max</i> (L.) Merr	Seeds	Aqueous extract	Wistar Rat (<i>Rattus norvegicus</i>)	Multi Low Dose Streptozotocin (MLD-STZ)	Not available	500, 750, 1000 mg/kgBW	750	65%	14 days	Gina et al. (2014)
Gnetaceae	<i>Gnetum gnemon</i> L.	Seeds	Ethanol extract	Male C57/BL6 mice	Streptozotocin	Not available	2% of powdered extract	-	extract did not change the plasma glucose levels	21 days	Ota et al. (2013)
Lamiaceae	<i>Clerodendrum fragrans</i> Willd	Leaves	Ethanol extract, ethyl acetate extract	White male rat (<i>Rattus norvegicus</i>)	Alloxan	Metformin 125 mg/kg	100, 200, 300 mg/kgBW	100	Reduced to 75.66 ± 3.18 mg/dL (no initial blood glucose level data)	14 days	Simorangkir et al. (2022)
Leguminosae	<i>Orthosiphon taminetus</i> Benth	Roots and leaves	Ethanol extract	Mice (<i>Mus musculus</i>)	Alloxan	Not available	35 and 50 mg/20 g BW/day	Leaves extract of 50 mg/20 gBW	41.6%	7 days	Andriaty et al. (2019)
	<i>Clitoria ternatea</i> L.	Flowers	Protein extract	male ddY mice	Alloxan	Metformin 100 mg/kg	100 and 500 mg/kgBW	500	55% Metformin 69%	30 days	Siahhaan et al. (2021)

Table 2 continued

Family	Species	Part of plant	Extract type	Experimental Animal	Induction of diabetes	Standard drug	Dose	Effective dose	Reduction	Time	Ref.
Lythraceae	<i>Lawsonia inermis</i> L.	Leaves	Hexane extract, ethyl acetate extract, ethanol extract, water infusion extract	male Wistar rats	Streptozotocin	Metformin 500 mg/kgBW	1000 mg/kgBW	Ethyl acetate extract 1000 mg/kg	36.5 ± 16% on the 3 h observation 77.9% metformin after 3 h	7 h	Widyawati et al. (2019)
Malvaceae	<i>Abelmoschus esculentus</i> (L.) Moench	Fruit	Aqueous extract	Male Swiss-Webster mice	Deficiency: alloxan Resistance: lipid emulsion	Deficiency: glibenclamide 0.65 mg/kg BW Resistance: metformin 135 mg/kgBW	both 25 mg/kgBW, 50 mg/kgBW, 100 mg/kgBW, and 200 mg/kgBW	Deficiency: 50 76 times Resistance: 50 and 100	Def: Gliben 67% 50 mg/kg bw 73% Resistance: 50 and 100 mg/kg bw 64% and 71% respectively (insulin sensitivity increase) Metformin: 78%	Both: 14 days	Alligita et al. (2019)
		seed	Steeping coffee from okra Oligomeric catechin (3,4 mg/g)	Mice	Alloxan	Not available	1.82, 3.64 and 5.46 mg/gBW/day	5.46 mg/gBW	47.7%	10 days	Munawwarah et al. (2019)
		Fruit	Ethanol extract	male Wistar rats	Alloxan	Novomix (insulin analog) 0.4 IU/100 gBW	75 mg/kgBW/day, 150 mg/kgBW/day, dan 300 mg/kgBW/day	No effective dose	okra extract can not reduce elevated blood glucose levels on Wistar rats	1 day	Prakoso et al. (2016)
Meliaceae	<i>Swietenia mahagoni</i> (L.) Jacq	Seeds	Ethanol extract	Rat	Sucrose	Acarbose 4.5 mg/kgBW	100, 200, 300, 400, and 500 mg/kgBW	None	Normal blood glucose levels for rats was maintained ranging between 90–142 mg/dL	2 h	Wresdiyati et al. (2015)
Menispermaceae	<i>Tinospora crispa</i> L.	Stem	70% Ethanol extracts	Wistar rat	Alloxan	Glibenclamide 0.63 mg/kgBW	500, 1000 and 2000 mg/kgBW	500	44.78% Glibenclamide: 39.43%	10 days	Sutrisna et al. (2018b)

Table 2 continued

Family	Species	Part of plant	Extract type	Experimental Animal	Induction of diabetes	Standard drug	Dose	Effective dose	Reduction	Time	Ref.
Myrtaceae	<i>Syzygium polyanthum</i> (Wight) Walp	Leaves	Methanol extract	Sprague Dawley rats (male)	Streptozotocin	Metformin 500 mg/kgBW	125, 250, 500 and 1000 mg/kgBW	250, 500, 1000 mg/kg showed antidiabetic activity in dose dependent manner comparable to metformin	Roughly 40–60% Metformin about 60%	6 days	Widaywati et al. (2015)
Oleaceae	<i>Olea europaea</i> L	Leaves	Aqueous extract	Wistar rats	Alloxan	Not available	540, 1080, 2160 mg / 200 gBW	2160	53.14%	3 days for the alloxan	Millati et al. (2019)
Oxalidaceae	<i>Averrhoa bilimbi</i> L	Leaves	Ethanol extract	Male wistar rats	Streptozotocin	Glibenclamide	15 mg	15 mg	42.16% Gliben: 51.07%	10 days	Wahyuni (2021)
Ranunculaceae	<i>Nigella arvensis</i> L	Seeds	Ethanol extract	Male wistar rats	Fructose	Metformin	24, 48 and 96 mg/kgBW		No significant elevation effect of insulin sensitivity	30 days	Panggabean et al. (2014)
Rosaceae	<i>Malus domestica</i> (Suckow) Borkh	Leaves	Ethanol extract (70%)	Sprague dawley rats	Alloxan	Metformin	200, 400, and 600 mg/kgBW	200	57.52 ± 9.67% (200 mg/kgBW) 75.99 ± 9.67% (metformin)		Yazid et al. (2021b)
Rubiaceae	<i>Morinda citrifolia</i> L	Fruits	Ethanol extract	Male white rats	Streptozotocin	glibenclamide 5 mg/kgBW	10, 20, 40 mg/kgBW	20	Blood glucose decrease: 48.3% Insulin increase: 55.6% Glibenclamide: 47.3% and 45.6%	7 days	Simulingga et al. (2018)
Scrophulariaceae	<i>Picris febrifera</i> Lour	Leaves	Ethanol extract	Rats	Alloxan	Lantus insulin 1 unit	200 and 300 mg/kgBW	300	72.28% Insulin: 66.2%	28 days	Widjaja et al. (2017)

date, several Indonesian medicinal plants traditionally used for diabetes management have been investigated for their antidiabetic activities through *in vivo* studies (Table 2). This review outlines 30 plant species from 26 botanical families that exhibit potential antidiabetic activity. Most of the *in vivo* studies employed crude extracts, while only two utilised plant fractions. Leaves were the most commonly used plant part, followed by roots, bulbs, peels, aerial parts, stems, fruits, seeds and flowers. Various solvents were used to prepare the crude extracts, with ethanol (67.86%) being the most common, followed by water (21.42%) and others (10.72%). The reviewed studies used animal models such as rats, mice and zebrafish. Diabetes was typically induced using alloxan and streptozotocin and the experimental duration varied from 2 h to 30 days. These *in vivo* studies primarily assessed the plants' ability to reduce blood glucose levels and enhance insulin sensitivity. Seven plant species from seven different families showed superior antidiabetic potentials compared to standard drugs used in the respective studies.

Centella asiatica (L.) Urb.

An *in vivo* study by Hayati et al. (Hayati et al. 2021a) evaluated the fasting blood glucose (FBG) lowering effect of an ethanolic extract of *Centella asiatica* (L.) Urb. leaves in zebrafish induced with alloxan and pretreated with 2% glucose solution for seven days. The leaves extract was formulated in a Self-NanoEmulsifying Drug Delivery System (SNEDDS) to improve its bioavailability (Hayati et al. 2021a). The study was conducted on five groups consisting of two groups of zebrafish treated with different doses (100 and 200 mg/2 L) of the *C. asiatica* ethanol extract SNEDDS groups, the positive and negative control groups, and the standard drug group which were observed for 12 h. Both doses demonstrated better FBG reduction of 69.90% and 72.20%, respectively, compared to 50 mg/L metformin as the standard drug (Hayati et al. 2021a).

Tithonia diversifolia (Hemsl.) A.Gray.

Among three species from the Asteraceae family, only the ethanolic leaves extract of *Tithonia diversifolia* (Hemsl.) A.Gray. showed significant FBG lowering effects (Yazid et al. 2021a). At a dose of 600 mg/kg, it

reduced FBG by 81.87% in alloxan-induced Sprague Dawley rats during 16 days of treatment, showing a better reduction compared to metformin as the standard drug. However, the study did not disclose the dose of metformin used, which limits the ability to perform a comprehensive analysis of the results (Yazid et al. 2021a). Furthermore, histological examination showed pancreatic tissue repairment with small-sized Langerhans islets and dominated by β -cells as compared to the normal, positive and negative control groups, suggesting protective effects against liver complications (Yazid et al. 2021a).

Sechium edule Sw.

Sechium edule Sw. (Cucurbitaceae), also known as chayote squash, has pharmacological effects as antidiabetic, antioxidant, anti-inflammatory, anti-obesity, anticancer, and hepatoprotective agents. Siahaan et al. (2021) reported the effects of its fruit ethanolic extract and ethyl acetate fraction in streptozotocin and nicotinamide induced albino rats. The ethyl acetate fraction at the dose of 100 mg/kg significantly reduced blood glucose levels by 60%, comparable to 40.5 mg/kg of metformin (60%) (Siahaan et al. 2021). This study also indicated that treatment with 100 mg/kg of ethanolic *Sechium edule* Sw. Fruit extract could stimulate insulin secretion and help protect pancreatic β -cells from degeneration by reducing oxidative stress (Siahaan et al. 2021).

Abelmoschus esculentus (L.) Moench

Aligita et al. (2019) evaluated the antidiabetic activity of *Abelmoschus esculentus* (L.) Moench fruit in Male Swiss–Webster mice models of insulin deficiency and insulin resistance. Commonly known as okra, this plant is one of the most widely used species in the Malvaceae family. Results showed that in the insulin deficiency group, oral administration of aqueous of *A. esculentus* fruit extract at concentration of 25, 50, 100 and 200 mg/kg resulted in reductions of blood glucose levels by 38%, 73%, 72%, and 64%, respectively, after two weeks of treatments. Among these, the 50 mg/kg dose displayed the most remarkable blood glucose-lowering effect, closely comparable to that of the standard drug glibenclamide (0.65 mg/kg), which produced a 67% reduction in blood glucose levels (Aligita et al. 2019). In the insulin resistance

group, treatment with the *A. esculentus* fruit aqueous extract at doses of 50 and 100 mg/kg significantly improved insulin sensitivity, with increases of 64% and 71%, respectively. The antidiabetic activity of *A. esculentus* fruit was attributed to enhanced insulin secretion and sensitivity, as well as the inhibition of intestinal carbohydrate absorption (Aligita et al. 2019).

Tinospora crispa L.

Tinospora crispa L. (Menispermaceae), commonly found growing wild in forests or cultivated in home gardens, is widely used in traditional Indonesian medicine to treat diabetes mellitus (Sutrisna et al. 2018a). The stem of *T. crispa* was extracted using 70% ethanol and reported to exhibit hypoglycemic effect in diabetic Wistar rats previously induced with alloxan. Administration of the extract at a dose of 500 mg/kg resulted in a 44.78% reduction in fasting blood glucose (FBG) levels. This dose produced the most significant glucose-lowering effect compared to higher doses (1000 and 2000 mg/kg) and was even more effective than the standard drug glibenclamide (0.63 mg/kg), which achieved a 39.43% reduction (Sutrisna et al. 2018b). Furthermore, histopathological examination of the pancreatic tissue from treated diabetic rats showed the absence of necrotic islet cells, indicating that the ethanolic stem extract of *T. crispa* may support the regeneration or protection of pancreatic islet cells (Sutrisna et al. 2018b).

Morinda citrifolia L.

Another study conducted on streptozotocin-induced diabetic male white rats demonstrated that the ethanolic extract of *Morinda citrifolia* L. fruits effectively lowered plasma glucose levels by increasing insulin secretion (Sinulingga et al. 2018). Diabetic rats were administered the extract at doses of 10, 20, 40 mg/kg, alongside a standard group treated with glibenclamide (5 mg/kg). Fasting plasma glucose levels and insulin secretion were monitored for seven days. Among the treatment groups, the 20 mg/kg dose of *M. citrifolia* L. fruit extract significantly reduced plasma glucose levels (48.3%) as compared to negative controls and was higher than the standard drug glibenclamide 5 mg/kg (47.3%) (Sinulingga et al. 2018). Similarly, this dose also induced the most significant increase in

insulin secretion, with a 55.6% elevation compared to the control group. The study attributed the antidiabetic activity of *M. citrifolia* to various bioactive compounds such as flavonoids, saponins, triterpenoids and triterpenes (Sinulingga et al. 2018).

Picria fel-terrae Merr

Picria fel-terrae Merr., a member of the Scrophulariaceae family, is widely distributed across Indonesia, including North Sumatra. It has been empirically used for treating diseases such as cancer, diabetes melitus, fever and malaria for years (Widjaja et al. 2017). In an in vivo study, Widjaja et al. (2017) evaluated the antidiabetic activity of the ethanolic extract of *P. fel-terrae* leaves in alloxan-induced diabetic rats. The results revealed that administration of the extract at doses of 200 and 300 mg/kg effectively reduced blood glucose levels, with the 300 mg/kg dose demonstrating a more pronounced effect than the 200 mg/kg dose. Furthermore, the 300 mg/kg dose of the ethanolic extract achieved a 72.28% reduction in blood glucose levels, surpassing the effect of the standard drug insulin, which produced a 66.2% reduction. (Widjaja et al. 2017).

Clinical studies of Indonesian antidiabetic medicinal plants

The indigenous people of Indonesia have practiced their traditional herbal medicine, known as *Jamu*, for centuries. *Jamu* is commonly prepared as decoctions or packed in a modernised form into capsules and tablets. Due to the long-term clinical uses of *Jamu*, the ingredients used were categorised as non-toxic products. Because of this established safety profile, the Indonesian government classifies many *Jamu* ingredients as non-toxic and low risk. Consequently, only well-known and traditionally used *Jamu* formulations are subject to simplified regulatory oversight, allowing them to proceed directly to clinical trials without extensive preclinical testing. A number of medicinal plants commonly used in *Jamu* have been prescribed to diabetic patients, and their effects on blood glucose levels have been clinically evaluated. These plants include, *Piper crocatum*, *Moringa oleifera*, *Muntingia calabura* L., *Swietenia mahagoni*, *Cinnamomum burmanii*, *Phaleria macrocarpa*, *Pandanus*

amaryllifolius roxb, *Syzygium polyanthum*, *Andrographis paniculata*, *Curcuma xanthoriza*.

Piper crocatum

Piper crocatum contains various bioactive compounds, including alkaloids, flavonoids, saponins, tannins and essential oils. Among these, flavonoids and alkaloids are believed to possess hypoglycaemic properties, potentially contributing to blood glucose reduction (Safithri and Fahma 2008; Suri et al. 2021). In one study, a 70% ethanol extract of *P. crocatum* leaves was administered to Wistar rats induced with diabetes mellitus (DM) using streptozotocin over a 21-day period. Rats treated with 50, 100, and 200 mg/kg body weight/day of the extract showed a significant reduction in fasting blood glucose levels compared to the control group, suggesting the antidiabetic potential of *P. crocatum* (Andhi 2016). Another study evaluated the effect of *P. crocatum* leaf decoction in alloxan-induced diabetic Sprague Dawley rats. After 10 days of daily administration at various doses, blood glucose levels were reduced by 10–38%. These findings further support the antihyperglycemic activity of *P. crocatum* in animal models.

A pre-post quasi-experimental study conducted in Madura, Indonesia, discovered that the use of *Piper crocatum* decoction significantly reduced blood glucose levels in patients with type II DM (T2DM). In this study, three *P. crocatum* leaves were boiled in approximately ± 600 mL of water until the volume was reduced by half (± 300 mL). Participants consumed approximately 100 mL of the decoction once daily after meals. The study was carried out in April 2017 and involved 18 adult T2DM patients aged 41–60 years, recruited from the Batuporo sub-district of Madura. Data were analysed using the paired sample T-test, and the results showed a statistically significant reduction in fasting blood glucose levels following the intervention. The mean blood glucose level decreased from 244.56 ± 28.73 mg/dL to 231.17 ± 28.88 mg/dL ($p < 0.000$) (Widiyono and Suwarni 2019). These findings, along with results from other in vivo and clinical studies, support the potential of *P. crocatum* as a supplementary herbal remedy to aid in the management and maintenance of normal blood glucose levels in diabetic patients.

Moringa oleifera Lam.

Moringa oleifera, a member of the *Moringaceae* family, is known as a nutrient-dense plant due to the high abundance of essential phytochemicals, vitamins, and micronutrients found in its leaves, pods, and seeds (Kasolo et al. 2010; Mbikay 2012; Rockwood et al. 2013). The leaves of *M. oleifera* contain a range of bioactive compounds, including alkaloids, saponins, phytosterols, tannins, polyphenols, sterols, phenolics, and flavonoids. These constituents exhibit strong antioxidant properties and are believed to contribute to its anti-cholesterol effect (Berkovich et al. 2013). Moreover, *M. oleifera* contains anti-cancerous substances such as glucosinolates, isothiocyanates, glycoside compounds, and glycerol 1-(9-octadecenoate). The flavonoids present in *Moringa* leaves have been shown to exhibit both antidiabetic and antioxidant activities, offering potential therapeutic benefits for individuals with hypercholesterolemia and hyperglycaemia (Gupta et al. 2012; Mbikay 2012).

A quasi-experimental study conducted in the Pakong sub-district of Madura, Indonesia, demonstrated that *M. oleifera* leaf powder significantly reduced blood glucose and cholesterol levels in participants. The study involved 40 obese adults (BMI > 25) aged between 18 and 40. Exclusion criteria included athletes, pregnant and breastfeeding women, and individuals taking medications such as antibiotics or weight-loss drugs. Participants were randomly assigned to either a treatment group or a control group. The treatment group received 500 mg of *Moringa* leaf powder daily, while the control group received only educational sessions on the prevention of hyperglycemia and hypercholesterolemia. Results showed a statistically significant reduction in mean fasting blood glucose levels in the treatment group, from 132.5 ± 42.1 mg/dL before the intervention to 119.4 ± 30.2 mg/dL after the intervention ($p = 0.009$). In contrast, the control group showed no significant change (pre-intervention: 178.1 ± 24.4 mg/dL; post-intervention: 175.95 ± 24.9 mg/dL; $p > 0.550$) (Denta et al. 2022). These findings are supported by a study conducted by Syamra et al. (2018), which reported that *M. oleifera* leaf decoction effectively reduced blood glucose levels in diabetic patients (Arleni and Andi 2018).

The flavonoids and alkaloids present in *M. oleifera* leaves contribute to its hypoglycaemic effects by promoting pancreatic β -cell regeneration and stimulating insulin release through both intra pancreatic and extra pancreatic mechanisms. Specifically, alkaloids are believed to stimulate sympathetic neurons, thereby increasing insulin release (Larantukan et al. 2014). Moreover, Divi et al. (2012) was effective in treating both streptozotocin (STZ)-induced Type 1 diabetes and insulin-resistant Type 2 diabetes in rat models. This suggests that the antioxidants compounds in *M. oleifera* play a crucial role in mitigating the oxidative stress caused by STZ-induced damage. The flavonoids in *M. oleifera* are thought to scavenge reactive oxygen species (ROS) released by mitochondria, thus protecting β -cells and keeping hyperglycemia under control (Al-Malki and El Rabey 2015; Kamalakkannan and Prince 2006).

The study conducted in Pakong sub-district of Madura, Indonesia, also discovered that after consumption of *M. oleifera* leaves powder significantly reduced cholesterol level in study participants. The mean total cholesterol level in the treatment group decreased from 187 ± 24.4 mg/dL to 173.3 ± 20.3 mg/dL ($p < 0.001$), while the reduction observed in the control group was not statistically significant (before: 184.3 ± 31.5 mg/dL; after: 182.55 ± 25.0 mg/dL; $p > 0.601$) (Denta et al. 2022). Supporting these findings, an animal study showed that treatment of *M. oleifera* leaves dose of 75 mg/kg resulted in a reduction of total blood cholesterol in rats by up to 47.5%. These results suggest that *M. oleifera* leaves powdered may serve as a natural agent for the prevention of hyperglycemia and hypercholesterolemia and may be beneficial as for diabetes mellitus and dyslipidemia.

Swietenia mahagoni (L.) Jacq.

A water decoction of *Swietenia mahogany* seeds has been traditionally used in Indonesia as a folk remedy for managing blood glucose levels (Kadota et al. 1990). Several studies have explored the therapeutic properties of *S. mahogany* seeds, examining their effects on blood glucose, insulin levels, and pancreatic tissue in diabetic animal models. The antidiabetic properties of its extract have been demonstrated through in vitro and in vivo experiments, as well as

in a limited number of clinical trials (Sukardiman and Ervina 2020).

The primary phytoconstituents found in the methanolic and aqueous extracts of *S. mahogany* seeds include tannins, alkaloids, saponins, terpenoids, anthraquinones, cardiac glycosides, and volatile oils (Sahgal et al. 2009). The methanolic *S. mahogany* seed extract (MEMS) has been shown to inhibit the α -glucosidase enzyme, thereby reducing the digestion and absorption of complex carbohydrates, and involving in the repair of damaged cells. One of its bioactive constituents, swietenin acts as a PPAR γ agonist, enhancing insulin secretion, promoting glucose uptake, increasing peripheral glucose utilization, and lowering blood glucose levels in diabetic models. Notably, the PPAR γ agonist activity of *S. mahagoni* extract at the dose of 1000 mg/kg was reported to be approximately half as effective as rosiglitazone in diabetic mice (Li et al. 2005). In addition, administration of MEMS reduced blood glucose and liver glycogen levels in streptozotocin (STZ)-induced diabetic rats. It also elevated antioxidant enzyme activity and reduced free radicals levels, indicating its potential for glycemic control and managing diabetes-related complications associated such as hyperlipidaemia and oxidative stress (Ghosh et al. 2011). Similar outcomes were observed when MEMS was compared to metformin in diabetic rats, suggesting its promise as a complementary or alternative therapeutic option (Bera et al. 2012).

Meanwhile, aqueous extracts of *Swietenia mahagoni* leaves (AEML) have also showed antidiabetic properties by reducing fasting BGL in diabetic rats. Additionally, a study discovered that both aqueous (AEML) and ethanol extracts of *S. mahagoni* (EEMS) exhibited α -glucosidase inhibitory activity, along with in vitro and in vivo hypoglycaemic effects at doses ranging from 100 to 500 mg/kg body weight (Wresdiyati et al. 2015; Yp and Urooj 2015).

Several studies have demonstrated the effectiveness of EEMS in reducing BGL through multiple proposed mechanisms, including boosting insulin secretion, decreasing food intake, reducing TNF- α levels, and preventing damage to pancreatic cells and the islets of Langerhans (Mahid-Al-Hasan et al. 2015; Suryani et al. 2013). In addition, Hajra et al. (2011) reported that the EEMS exhibited α -amylase inhibitory activity in vitro, supporting its antidiabetic potential. In diabetic rat models, EESM showed a

relatively stronger antidiabetic effect than the standard drug glibenclamide. Notably, Sukardiman et al. (2017) found that its glucose-lowering surpassed that of glibenclamide in a dose-independent manner. This study guided the development of *S. mahagoni* seed extract into pharmaceutical formulations, with a dried preparation composed of mahogany extract, Avicel, and Cab-O-Sil in a 70:30 ratio, subsequently dried at a 4:1 ratio (Sukardiman and Ervina 2020). The antidiabetic activity was attributed primarily to the flavonoid and saponin content of the extract. Furthermore, an increase in total haemoglobin (Hb) and a decrease in glycosylated Hb levels were observed following treatment. Histological and biochemical analyses of the pancreas confirmed these findings, indicating that the extract's antidiabetic mechanism involved enhanced insulin secretion (Kalaivanan and Pugalendi 2011; Kurniawati et al. 2010).

A more recent clinical study of *S. mahagoni* was performed in 68 patients with type 2 diabetes (T2D) using an experimental pre- and post-test control group design. The results showed that 85.3% of participants in the treatment group achieved blood glucose levels within the range of 90 to 199 mg/dL. Based on bivariate analysis, *S. mahagoni* seed demonstrated significant potential in reducing BGL when compared to glimepiride (Astuti 2017).

Collectively, various extracts of *S. mahagoni* seed have exhibited antidiabetic activities through several mechanisms, including lowering BGL, suppressing α -amylase and α -glucosidase activity, restoring liver and pancreatic islet function, and possessing antioxidant and antihyperlipidemic effects.

Cinnamomum burmannii (Nees & T.Nees) Blume

Indonesian cinnamon (*Cinnamomum burmannii*), a traditionally used spice, has been extensively studied for its pharmaceutical potential and rich phytochemical constituents. Its key chemical constituents include cinnamyl alcohol, cinnamaldehyde, coumarin, cinnamic acid, anthocyanin, flavonoids and essential oils (Al-Dhubiab 2012). The active substance in cinnamon bark, particularly polyphenols from flavonoids, are known to enhance insulin sensitivity and reduce blood glucose levels by augmenting insulin receptors. However, in vitro and in vivo studies specifically validating these effects for *C. burmannii* remain limited.

The blood glucose-lowering mechanism of *C. burmannii* can be explained by the evidence that cinnamon polyphenol extracts exhibit insulin-like and insulin-independent effects on gene regulation in mouse adipocytes. Cao et al. (2010) investigated the effect of *Cinnamon* extract (CE) on gene expression in cultured mouse adipocytes and discovered that CE modulated the expression of adipokines, upregulated *GLUT1*, and influenced components of the insulin signaling pathway. Additionally, a study examined the effects of standardized extract combination containing *Lagerstroemia speciosa* and *C. burmannii* (DLBS3233) on glucose homeostasis in rats and insulin-resistant Wistar rats. The results demonstrated that DLBS3233 enhanced tyrosine phosphorylation of the insulin receptor substrate and upregulated genes involved in insulin signalling and sensitivity. This extract also promoted glucose uptake, increased adiponectin secretion, and decreased resistin levels (Tandrasasmita et al. 2011).

Several studies conducted in Indonesia have investigated the potential of *C. burmannii* in reducing blood glucose levels. A clinical experimental study involving 20 diabetic patients revealed a significant reduction in blood glucose levels following the consumption of *C. burmannii* bark decoction for one week (Fatmalia 2017). More recently, a study in Makassar, Indonesia, involving individuals with prediabetes found that cinnamon bark administration over 14 days significantly lowered fasting blood glucose levels (Jafar et al. 2020). In addition, a study conducted in Portugal indicated that cinnamon tea might help regulate glucose metabolism in nondiabetic adults during the postprandial period. The study observed a slight decrease in postprandial blood glucose levels, resulting in a reduced maximum glucose concentration and less fluctuation after meals (Bernardo et al. 2015). However, contrasting results were reported in a randomized controlled trial indicated that administering an aqueous cinnamon extract (6 g/100 mL) to adults with type 2 diabetes mellitus (T2D) did not significantly influence postprandial glucose response during an oral glucose tolerance test (OGTT) (Rachid et al. 2022).

Furthermore, a systematic review and meta-analysis concluded that supplementation with *C. burmannii* significantly reduced fasting blood sugar (FBS) by an average of 19.26 mg/dL, while no significant changes in other glycaemic parameters or anthropometric

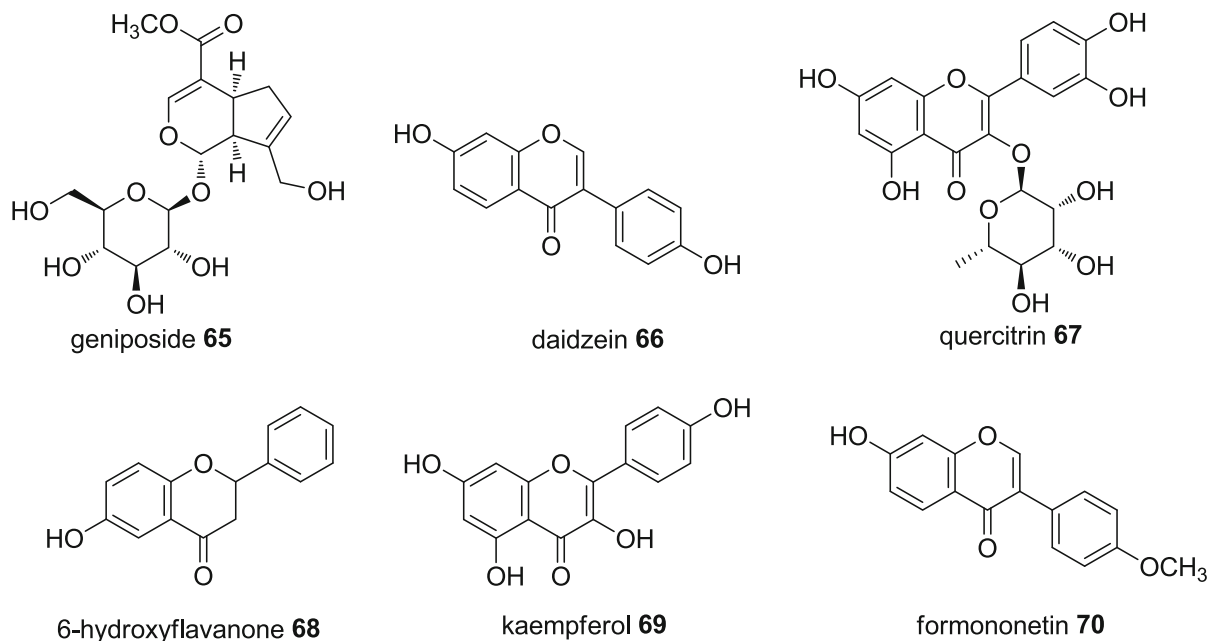


Fig. 16 Antidiabetic active constituents of Indonesian *M. calabura*

indices. Additionally, serum insulin levels and insulin resistance remained unaffected (Namazi et al. 2019).

Muntingia calabura L.

Muntingia calabura, a plant commonly found in Indonesia and other tropical regions, has been used in the form of leaves decoction to manage diabetes. However, the hypoglycaemic activity and potential benefits of this plant in diabetes management have only been reported in a limited number of studies. An in vitro study was carried out to investigate the bioactive compounds and antidiabetic activities of *M. calabura* leaves. The extract exhibited strong α -glucosidase and α -amylase inhibitory activities. Through UHPLC-ESI-MS/MS analysis, 61 compounds were tentatively identified in the most active extract. Further quantitative analysis using UHPLC revealed that geniposide 65, daidzein 66, quercitrin 67, 6-hydroxyflavanone 68, kaempferol 69, and formononetin 70 were the predominant constituents present in the active extract (Fig. 16) (Zolkeflee et al. 2022).

An in vivo study on hyperglycemic rats investigated the effect of *Muntingia calabura* ethanol extract (450 mg/kgBW) on blood glucose levels. The extract significantly reduces blood glucose, with results

comparable to the group treated with metformin. The bioactive compounds present in *M. calabura* L were reported to support the regeneration of pancreatic β -cells, enabling insulin production to help maintain normal glucose level (Andalia et al. 2021). A similar result was observed in a separate study using a water extract of *M. calabura* leaves administered at a dose of 400 mg/kgBW to insulin-deficient and insulin-resistant animal models. In the insulin-deficient model, the extract significantly reduced FBG levels, while in the insulin-resistant model, it improved the insulin tolerance constant. The study concluded that the water extract *M. calabura* leaves at 400 mg/Kg bw exerted antidiabetic activities through multiple mechanisms, including lowering blood glucose level, regenerating pancreatic β -cells, and enhancing insulin sensitivity (Aligita et al. 2018). The antidiabetic potential of *M. calabura* fruit (100 mg/kg) was investigated in streptozotocin (STZ)-induced diabetic rats. The study demonstrated that the fruit extract significantly reduced blood glucose levels, implying its potential as a complementary therapy alongside conventional antidiabetic drugs (Pramono and Santoso 2014). In addition, a quasi-experimental study involving 15 patients with T2D was conducted to assess the effect of *M. calabura* fruit on blood glucose levels. The results revealed a significant reduction in the patients'

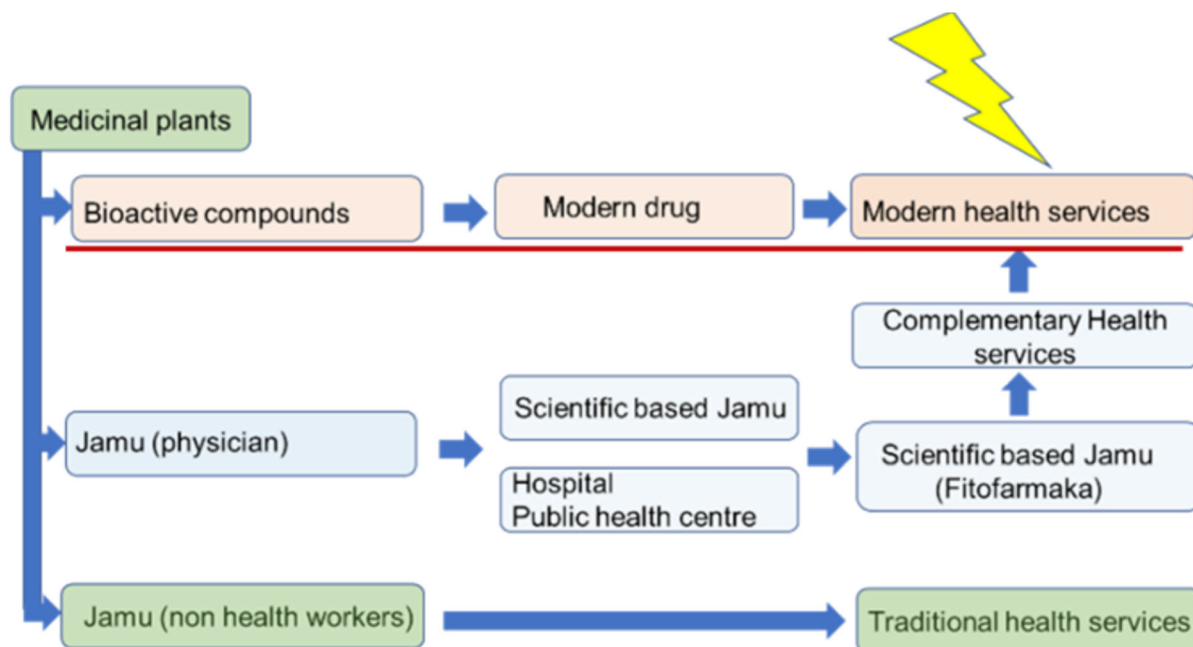


Fig. 17 Herbal medicine-based drug development in Indonesia (Rani et al. 2023)

average blood glucose levels following the intervention (Agustina and Samsul Bahri 2016).

Antidiabetic formula

An herbal-based medicine was prepared as a formula combining several plant ingredients for synergistic effects. The formulation consisted of 5 g *Syzygium polyanthum* leaves, 5 g *Andrographis paniculata* herbs, 7 g *Cinnamomum burmani* barks, and 10 g *Curcuma xanthoriza* rhizomes. A clinical study involving 242 volunteers was conducted to evaluate the formula's efficacy. Participants were divided into two groups: one received the herbal decoction twice daily, while the other was treated with oral metformin for six weeks. At baseline (day 0), the fasting blood glucose (FBG) levels were 162.92 in the decoction group and 164.37 mg/dL in the metformin group. By day 21, the average FBG levels had decreased to 155.37 mg/dL and 154.87 mg/dL, respectively. Notably, at the end of the study (day 42), the FBG level in the decoction group further decreased to 149.11 mg/dL, whereas the metformin group showed a level of 162.92 mg/dL. These results suggest that the herbal formula demonstrated a more pronounced anti-hyperglycemic effect over the medium term compared to the conventional drug treatment (Astana and Nisa 2021).

Indonesian Government policies toward modern herbal medicine regulation and development

One of the major challenges facing the pharmaceutical sector in Indonesia is its heavy reliance on imported pharmaceutical raw materials, which accounts for approximately 90% of the total supply, with an estimated annual value of around 13 trillion rupiah (Indonesia 2015). The Covid-19 pandemic further emphasized the need for national health resilience, prompting the government to strengthen policies aimed at achieving greater self-sufficiency in healthcare services, including domestic medicine production (Indonesia 2021b). Drug development policies in Indonesia are outlined in the National Research Master Plan, which is operationalized in the National Research Priorities. One of its strategic focus areas is health, particularly in research and technology to produce medicinal preparations derived from natural raw materials. This includes the development of standardized herbal medicine ingredients and phytopharmaceutical products (Fig. 17) (Indonesia 2019). The implementation of these policies has actively encouraged research and innovation in the development of phytopharmaceuticals to support and reinforce the domestic pharmaceutical industry (Indonesia 2021a). To date, records indicate that 26

phytopharmaceutical products have successfully demonstrated their safety and efficacy through comprehensive preclinical and clinical evaluations (Indonesia 2021a).

The National Agency of Drug and Food Control in Indonesia classifies herbal medicine into three categories: *jamu*, *obat herbal terstandar* (OHT) and *fitofarmaka*. *Jamu* refers to traditional Indonesian herbal medicines whose safety and efficacy are supported by empirical use, with over 12,000 registered products currently available. *Obat herbal terstandar* (OHT) are standardized herbal medicines with scientifically validated safety and efficacy through preclinical studies, with 86 products officially registered. Meanwhile, *fitofarmaka* represents the highest category of herbal medicines whose safety and efficacy have been confirmed through preclinical and clinical trials, with a total of 26 registered products as of 2021 (RI 2021). Despite Indonesia's rich biodiversity and favorable tropical climate, which provide an abundant and sustainable source of medicinal plant materials, natural product-based pharmaceuticals remain a relatively minor segment within the country's 202 pharmaceutical industries. Nevertheless, the development of *fitofarmaka* has become a national priority in the advancement of natural product-based therapeutics, particularly for chronic diseases such as diabetes. (RI 2021). To support this, the Indonesian government actively promotes research and innovation, encouraging start-ups and pharmaceutical companies to develop scientifically grounded, natural ingredient-based products capable of becoming mainstream pharmaceutical options, including *fitofarmaka* for diabetes therapy.

One of the major challenges in development of *fitofarmaka* is the prevalence of misinformation, which has led some health practitioners to dispense herbal products alongside conventional medicine without adequate scientific validation. On the other side, the Indonesian government has taken steps to promote the responsible and evidence-based use of herbal medicines through initiatives such as the establishment of *Klinik Herbal*, a dedicated herbal medicine clinic located in Karanganyar Regency-Central Java (Indonesia 2010). Managed by the Ministry of Health, this clinic serves as a platform to introduce and promote the clinical application of herbal-based medicines to both general practitioners and the wider public (Indonesia 2010). Since its

establishment, the number of patients visiting Klinik Herbal has steadily increased, particularly among those seeking alternative or complementary therapies for chronic conditions such as diabetes and other metabolic disorders (Indonesia 2010). Notably, this clinic is the first of its kind in Indonesia, employing a multidisciplinary team comprising researchers, medical doctors, and pharmacists. Furthermore, it remains accessible to the public at no cost, making herbal-based healthcare services more widely available and supporting the government's efforts to integrate scientifically validated herbal medicines into national health services (Indonesia 2010).

Despite the government's development focus on *fitofarmaka*, several policies have also been established to ensure the quality and safety of other forms of herbal-based medicines, particularly *Jamu*, which remains the most widely produced and consumed traditional medicine in Indonesia, despite historically limited regulations (Indonesia 2022). To address this, the government introduced Good Manufacturing Practices for Traditional Medicines (GMP-OT)—a set of enforced production standards specifically designed for herbal medicines, including *jamu*. This protocol is tailored to small-scale production, making it suitable for local industries and even home-based enterprises (Indonesia 2022). These traditional medicine industries play a significant role in the national economy, employing millions of people (Makanan 2023). However, one of the primary challenges faced by small-scale producers is maintaining hygiene standards, with approximately 80% of these industries reportedly encountering issues in this area. In response, the government has provided incentives, training programs, and technical support to help improve hygiene practices and production quality. Financial assistance and facilitation have also been made available to ease the financial burden on small enterprises in meeting these standards (Makanan 2023).

Overall, alongside these regulatory and capacity-building efforts, the government continues to actively encourage research aimed at the discovery and development of new phytopharmaceuticals, with the long-term goal of positioning them as a leading component of the country's pharmaceutical sector.

Conclusions

Diabetes remains one of the major public health burdens in Indonesia. Due to limited accessibility, affordability, and sometimes limited effectiveness of conventional Western medicines, many Indonesians continue to rely on traditional and herbal remedies for managing various types of diabetes, especially T2D. Numerous scientific studies have demonstrated that these medicinal plants exhibit a wide range of antidiabetic activities, from mild to potent effects. In *in silico* studies, compounds such as gartanin, quinine, and quinine have been identified as promising SIRT1 activators with potential antidiabetic properties. Furthermore, both *in vitro* and *in vivo* investigations have revealed strong antidiabetic activities in plant species such as *Cordia myxa*, *Merremia mammosa*, *Antidesma bunius*, *Antidesma montanum*, *Lunasia amara*, *Phaleria macrocarpa*. Several traditional herbal formulations from the mixture of *Centella asiatica*, *Tithonia diversifolia*, *Sechium edule* Sw., *Abelmoschus esculentus*, *Tinospora crispa*, *Morinda citrifolia*, *Picria fel-terrae* have also demonstrated notable antidiabetic activities. Interestingly, several medicinal plants, including *Piper crocatum*, *Moringa oleifera*, *Muntingia Calabura L.*, *Swietenia mahagoni*, *Cinnamomum burmannii*, *Phaleria macrocarpa*, *Pandanus amaryllifolius roxb.*, *Syzygium polyanthum*, *An-drographis paniculata*, *Curcuma xanthoriza* have been tested in the health clinics involving small groups of diabetic patients. These trials reported significant improvements in glycemic control, highlighting their potential as alternative therapeutic options for T2D management. Despite these promising findings, many Indonesian medicinal plants with potential antidiabetic properties remain unexplored. In response, the Indonesian government has recently introduced updated regulations, supportive policies, and increased research funding to encourage the systematic exploration, validation, and development of these traditional resources into scientifically based modern medicines.

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Declarations

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