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Indonesia Herbal Medicine and Its Active Compounds for Anti-diabetic Treatment: A Systematic Mini Review

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Abstract: We reported the systematic review of anti-diabetic herbal medicine from Indonesia by integrating herbal medicine databases and summarized the anti-diabetic compounds in Indonesian plants. We used data sources from Pubmed and local Indonesian databases such as Portal Garuda and Basis Data Tanaman Obat Indonesia (BDTOI) to elucidate anti-diabetic candidate herbal medicine. We found 927 articles (PubMed) and 70 articles (Portal Garuda) based on the criteria of anti-diabetic properties. After thoroughly assessing those publications, 38 articles on controlling blood glucose were identified. Moreover, we utilized ClinicalTrial.gov to map the evidence. Five species (*Abelmoschus esculentus*, *Allium sativum L*, *Cinnamomum cassia*, *Citrullus colocynthis*, and *Punica granatum L*) passed the clinical trial, three of which were intended for use in treating other diseases, and eight of which lacked clinical evidence. Additionally, over 30 compounds were elucidating from those herbs, including quercetin and allicin. In conclusion, we successfully retrieved anti-diabetic herbal medicine from Indonesia by integrating public databases. The molecular docking study was employed to predict and optimize the anti-diabetic outcomes.

Keywords: Anti-diabetic; Herbal remedies; Medicine; Natural compounds; Indonesia

1. Introduction

Medicinal plants remain the foundation for research in an era where new drugs are being developed. When performed in the laboratory with experimental animals, screening the pharmacological activity of the active ingredients in medicinal plants is expensive and takes time, energy, and qualified human

resources (Petrovska *et al*., 2012). Recently, using databases as tools in drug research has been an appealing possibility (Mohs & Greig, 2017). Due to their distinctive characteristics, herbal medicines are crucial molecules in the study of medicine, chemistry, and society. Compounds produced from natural products derived play a vital role in medication development. The biological property and chemical structures encourage their use as the initial structures for drug discovery. The effectiveness of the screening methods depends on the caliber and variety of the chemical libraries. Over 10,000 biological targets have seen a dramatic surge in combinatorial compounds over the past two decades. Drug discovery problems can be partially resolved by employing combinatorial molecules, but their potency and variety are constrained (Mario *et al*., 2003). Despite having a wide range of physicochemical characteristics and structures, many natural products derived compounds fail to meet the requirements for being leadlike and druglike (Butler, 2008).

One of the most concerning health statistics worldwide is the epidemic surge in the number of new cases of diabetes. The most concerning aspect of this observation is the emergence of chronic condition effects (Cefalu *et al*., 2011). On a clinical level, the main goal was to construct a regimen for a diabetic patient that would improve the metabolic parameters linked to the onset and progression of problems. As a result, it is widely acknowledged that one of the key strategies was to attain the target levels for glycemia, lipids, and blood pressure that have been advised. This approach may involve a lifestyle change, but it is most frequently a combination of dietary changes and increased physical activity with pharmaceutical intervention from medications from various groups (Riddle, 2005). Patients may add dietary supplements to their treatment plan in various ways, such as vitamin and mineral blends. However, the most common supplements patients take are thought to be made from natural sources, such as herbs or botanicals. Recently, the creation of information systems has been complicated in the modern world despite the hegemony of the information age having dynamized the revolution of ethnopharmacological data in terms of storage, management, and dissemination (Cordell, 2019). Various medical cultures have reported different therapeutic benefits of a specific herb.

Consequently, a plant may be recognized by various identities and characteristics. There are many herbal medicines available for the treatment of diabetes (Skalli *et al*., 2019; Loukili *et al*., 2022; Rahman *et al*., 2022; Ouahabi et al., 2023; Yedjou et al., 2023). However, not all herbs are thoroughly explored for one cause or another.

In this paper, we are enthusiastic about investigating the possibilities of studying Indonesian herbal medicine by integrating a national and international database to identify anti-diabetic compounds in Indonesian plants used for herbal remedies. In addition to the theoretical study of molecular docking, it is crucial to examine the stability of the complexes within the active site of the α-amylase as a key therapeutic target of diabetes.

2. Methodology

This study was carried out based on a combination of literature studies. The research flow is presented in **Figure 1**. We used the PubMed and Portal Garuda databases with specific the last ten years publication. The data was downloaded in November 2022 by typing the keyword "*Anti-diabetic* AND *Extract*." This systematic review focuses only on anti-diabetic herbal medicine extract and its active compounds. The article with the same title and plant was ejected in this review. After the data was obtained, then overlapped with BDTOI (Yanuar *et al*., 2011) to ensure that the plant originally came from Indonesia—further, identification of active compounds with anti-diabetic properties in herbal medicine.

3. Molecular Docking Studies

3.1. Ligand library collection and preparation

The library of compounds selected for their anti-diabetic properties, obtained from Indonesian plants used in herbal remedies, was retrieved from the PubChem database (http://pubchem.ncbi.nlm.nih.gov) in the 3D coordinates of Structure Data File Format (SDF). The three-dimensional structures (3D) of these compounds, along with the ligand Acarbose, used as a control, were prepared for molecular docking studies. 3D and geometric optimizations, along with ligand energy minimization, were performed using controlled algorithms in Schrödinger 2021-2 (Merzouki *et al*., 2023). The LigPrep module was utilized to add hydrogen atoms, eliminate salts, and perform ionization at pH 7 ± 2. Energy minimization was accomplished using the OPLS4 force field.

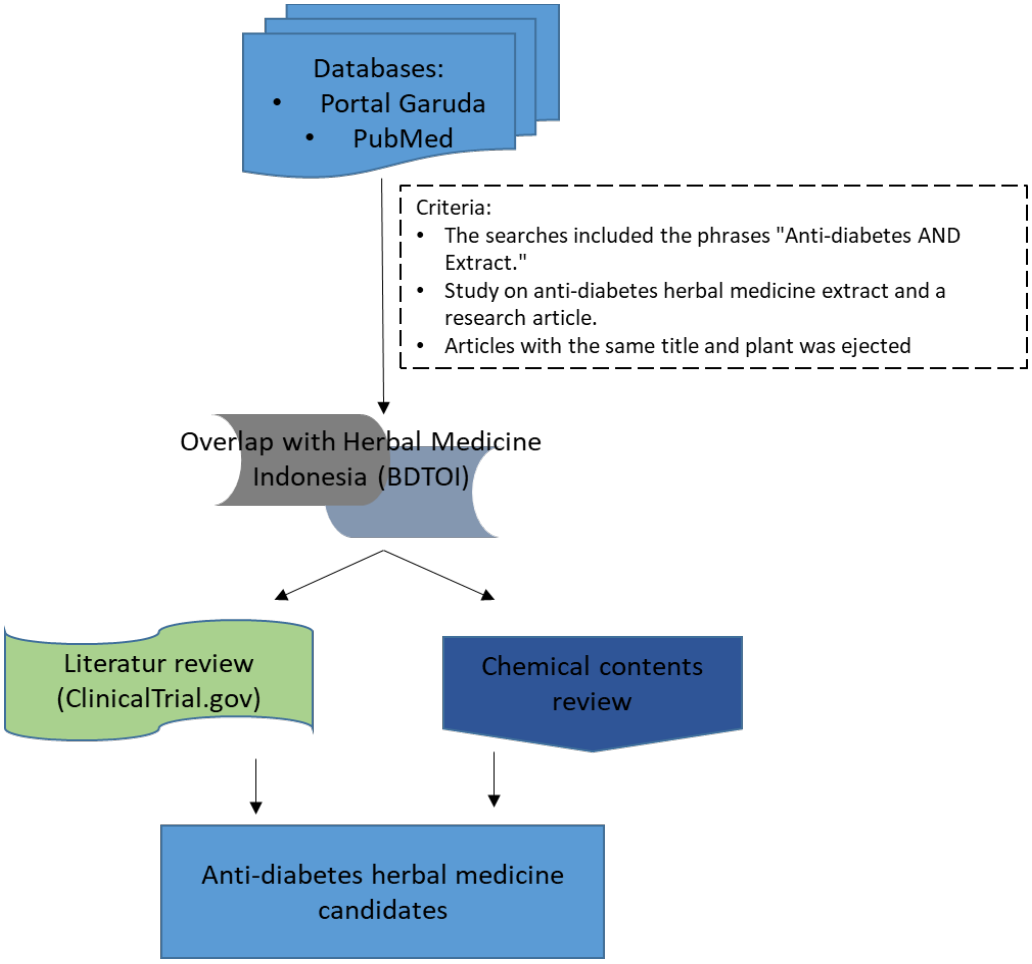


Figure 1. The research flow to find anti-diabetes herbal medicine candidates by combining several databases.

3.2. Protein preparation and molecular docking

Molecular docking of α-amylase was conducted using the X-ray crystal structure of human pancreatic α-amylase complexed with mini-montbretine A (PDBID: 5E0F) **Figure 2** with a resolution of 1.40 Å. The protein structure was prepared using the Protein Preparation Wizard (Schrodinger 2021-2) with ligand and water atoms removed, and non-polar hydrogens were merged. The active site where α-amylase binds with mini-montbretine A was selected as the docking center. The grid box site in α-amylase was fixed at x=-8.29 Å, y=21.6 Å, and z=-18.72 Å, employing the extra Precision (XP) glide score to predict binding free energy and ligand strain energy, and to select docked poses. Output docking scores were expressed as affinity binding (Kcal/mol) (Diass *et al*., 2023). Energy minimization

was performed using the OPLS4 force field with an RMSD limit of 0.3 Å by default. Finally, the structure of the protein was minimized, and the conformation with the lowest binding energy was chosen. The selected conformation was converted into bidimensional diagram to illustrate the interaction of the ligand with the active site residues.

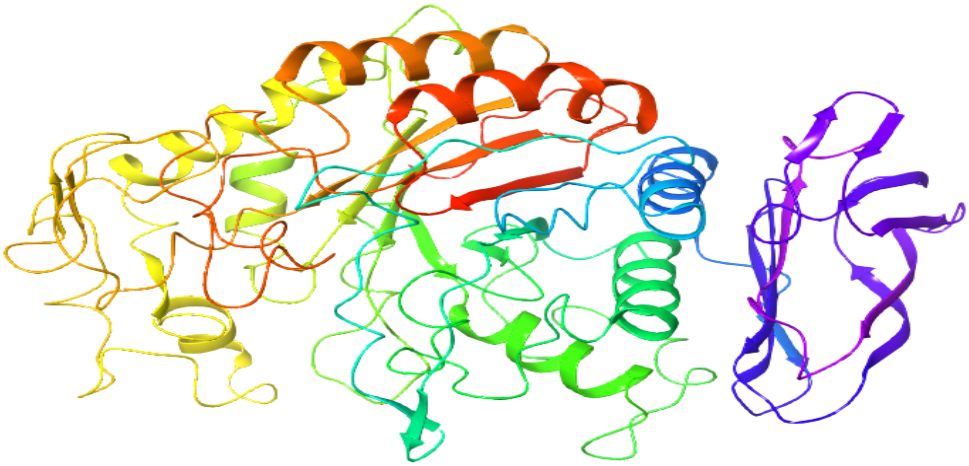


Figure 2. The three-dimensional structure of the α-amylase protein.

4. Results and Discussion

The typical pharmaceutical industry is currently in a dilemma because, despite significant increases in investment over the past few years, the number of truly innovative new drugs that the US Food and Drug Administration approves each year has not increased in line with those increases (Munos, 2009). Due to their multi-component and multi-function characteristics, evaluating herbal mixture pharmacological and toxicological effects is challenging. The observation via the framework of systems-based approaches would be more appropriate (Ru *et al*., 2014).

We obtained 20 articles in Portal Garuda and 18 in PubMed was matching the inclusion and exclusion criteria (**Table 1**). The BDTOI is a medicinal plant database of natural compounds in Indonesia. We overlapped the data with BDTOI (**Table 1**). We found 17 species matched with BDTOI for both Portal Garuda and PubMed databases. The species elucidated from Portal Garuda such as *Allium sativum L, Cinnamomum cassia, Citrullus colocynthis, Trigonella foenum graceum, Coffea Arabica, Elephantopus scaber L, Eleutherine Palmifolia (L.,), Hibiscus rosa-Sinensis L, Hydnophytum formicarium, Momordica charantia, Morinda citrifolia, Muntingia Calabura L, Musa Paradisiaca Var Kepok, Persea Americana Mill.,* and *Sechium edule*. Meanwhile, the species obtained from PubMed include *Abelmoschus esculentus, Pennisetum glaucum L*, and *Punica granatum L*.

Furthermore, we check whether those species matched with BDTOI are under clinical trial for diabetes by overlapping it with https://clinicaltrials.gov/. The result demonstrated that five species passed the clinical trial, three passed the clinical trial for other diseases, and eight did not have evidence (**Table 2**). Five species identified for anti-diabetic such as *Abelmoschus esculentus, Allium sativum L, Cinnamomum cassia, Citrullus colocynthis*, and *Punica granatum L*. Dubey and co-workers examined the use of *Abelmoschus esculentus* (Okra or Bendi) in the management of diabetes, with a focus on the ability of the species to lower blood sugar levels. They reported that Okra could control elevated blood glucose concentration in traditional medicine and that years of contemporary research have correlated this traditional claim with scientific evidence (Dubey & Mishra, 2017). Its activity has correlated with the quercetin derivative inside of Okra. The other compounds, such as isoquercetin and quercetin, are

two flavonol glucosides reported by prior research as active compounds in inhibiting glucosidase (Thanakosai & Phuwapraisirisan, 2013).

We obtained that most clinical research has shown garlic could control lowers blood glucose levels, but not in diabetic patients. The impact of garlic on reducing human blood sugar levels has yielded varied results. Some studies found garlic ineffective in decreasing blood glucose levels. However, a study by Isnaeni *et al.* (2019) reported different findings. They discovered that garlic can lower blood glucose levels and several important indicators, such as HbA1c. Foroozand *et al.* (2023) also revealed that garlic reduces glucose, cholesterol, LDL, triglyceride, and HDL levels. Effect of garlic hypoglycemic may result from increased pancreatic insulin secretion from beta cells, the release of bound insulin, or improved insulin sensitivity (Al-Ishaq *et al.*, 2019).

Moreover, Allicin, an active ingredient extracted from garlic, improved fat accumulation, body weight, and blood glucose, preventing AGE development in rats. Allicin treatment also reduced AGE (Advanced Glycation End products) activity by inhibiting RAGEs (Receptors of Advanced Glycation End products) which reduced oxidative stress and increased insulin secretion (Li *et al*., 2022). It is well known that AGEs, also known as glycotoxins, are a class of dangerous chemicals that are highly heterogeneous and complicated and are formed by nonenzymatic chemical interactions between proteins and reducing sugars or lipids (Uribarri *et al*., 2010). The chemical structure of Allicin is present in **Figure 3**.

Cinnamon has demonstrated significant benefits in aiding individuals with type II diabetes to manage their condition. It seems to assist in regulating and stabilizing the blood glucose levels of diabetic patients with impaired insulin responsiveness (Baker *et al*., 2008; Pham *et al*., 2007). The specific compound in cinnamon that contributes to its insulin-like effects is still debatable. Initially, methyl hydroxy chalcone polymer (MHCP) (**Figure 3**) was identified as the component responsible for reducing blood glucose levels, possibly by acting as a molecular mimic. In the laboratory, MHCP has been shown to activate cell receptors, potentially including insulin receptors (Jarvill-Taylor *et al*., 2001). However, recent suggestions propose that the polyphenols present in cinnamon, particularly polyphenol A, may also play a role in lowering blood glucose levels (Davis & Yokoyama, 2011). Another intriguing study revealed that cinnamon supplementation might be just as efficient at regulating HbA1C levels as some oral diabetic medicines (Hoehn & Stockert, 2012).

The Cucurbitaceae family plant *Citrullus colocynthis* has a long history of use as an anti-diabetic medication. It is frequently referred to as bitter apple or cucumber and is prized for its therapeutic qualities worldwide, especially in Indonesia (Rahimi *et al*., 2012). The pulp of *Citrullus colocynthis* contains significant amounts of galacturonic acid and colocynthin derivatives (**Figure 2**). The seeds yield albuminoids and fixed oil. Cucurbitacins and flavones, however, are considered to be this plant's primary constituents and to have a therapeutic role in its function (Abdel-Hassan *et al*., 2000). The last herbal remedies that found in our study is *Punica granatum L*. Traditional Asian medicine places a high value on pomegranate (*Punica granatum L*., *Punicaceae*) for treating various health problems. This plant is known as "dalima" (fruit) in Ayurvedic medicine. It is a blood purifier with applications in treating parasite infections, mouth ulcers (aphthae), diarrhea, and ulcers (Jurenka, 2008). Although corilagin, ellagic acid, kaempferol, luteolin, myricetin, quercetin, quercimetrine, and quercetin-3-o-rutinoside are among the significant active chemical constituents and phytoconstituents of *Punica granatum*, recent research indicates that valoneic acid dilactone (**Figure 3**) was the chemical compound that contributes to anti-diabetic activity (Jain *et al*., 2012).

In this review, we identified over 30 active compounds in Indonesia herbal medicine for anti-diabetic treatments, such as damnacantol-11-O-beta-primeveroside, gartanin, vindolinine, salvigenin,

ursolic acid, spatozoate, curcumin, vindolicine, episesamin 2,6-dicatechol, tetramethylscutellarein, lirioresinol B dimethyl ether, orthosiphol A, lucidin 3-O-beta-D-primeveroside, 3,7,4'-tri-O-methyl-kaempferol, quercetin, sinensetin, isoquercetin, kaurenoic acid, demethoxycurcumin, vindoline, rutin, ursonic acid, bisdemethoxycurcumin, γ-mangostin, smeathxanthone A, (E)-2-amino-3,4,14-trihydroxy-2-hydroxymethyleicos-6-enoic acid, lirioresinol B, vindolidine, 3-hydroxy-11-ursen-28,13-olide, deoxyandrographolide, ar-turmerone, α-mangostin, colocynthin, valoneic acid dilactone, galacturonic acid, allicin, and methylhydroxy chalcone (**Figure 3**).

Table 1. Research articles related to inclusion and exclusion criteria of Portal Garuda and PubMed.

No.	Research article title	Plant	Ref.
Portal Garuda (Indonesian Local Database)			
1	Ethanol extract and hexane fraction of *Momordica charantia* decrease blood glucose level of diabetic rat	*Momordica charantia*	Suartha *et al*., 2016
2	Anti-diabetic Activities of *Muntingia Calabura L*. Leaves Water Extract in Type 2 Diabetes Mellitus Animal Models	*Muntingia Calabura L*	Aligita *et al*., 2018
3	The influence water extract of black soybean (*Glycine max (L.) Merr.*) on reducing of blood glucose level and the superoxide dismutase (SOD) activity on diabetes mellitus rats induced with multiple low dose of streptozotocin (MLD-STZ)	*Glycine max (L.) Merr.*	Gina & Mahdi, 2014
4	The Effect of Dayak Onion Bulb-Stem (*Eleutherine palmifolia (L.,) Merr.*) Extract on Blood Glucose Levels of Mouse Suffered Diabetes Mellitus	*Eleutherine Palmifolia (L.)*	Arwati *et al*., 2018
5	Hypoglycemic effect of banana peel extract (*Musa Paradisiaca Var Kepok*) in New Zealand White Diabetes Hyperlipidemia	*Musa Paradisiaca Var Kepok*	Samiasih *et al*., 2018
6	Effectiveness of Ethanol Extract of Avocado Seeds (*Persea americana mill*.) on Blood Glucose Levels of Male White Rat (*Rattus novergicus*) Hipercolesterolemia-diabetes Model	*Persea Americana Mill.*	Patala *et al*., 2020
7	*Hibiscus rosa-Sinensis* L. Extract Improves Fasting Blood Glucose Levels and Number of Mast Cells in Diabetic Rat Model that Infected with Mycobacterium tuberculosis	*Hibiscus rosa-Sinensis L*	Pakaya *et al*., 2020
8	Effect of Noni Fruit Extract (*Morinda citrifolia*) on Glucose Intake to Diabetes Mellitus White Rat Muscle Tissue	*Morinda citrifolia*	Wulandari, 2020
9	The Potency of *Sechium edule* Ethanolic Extract to Repair Beta Pancreas Cells and Nitrogen Oxide Concentration in Streptozotocin-induced Diabetic Rat	*Sechium edule*	Lukiati *et al*., 2016
10	Effect of Black Garlic Extract on Blood Glucose, Lipid Profile, and SGPT-SGOT of Wistar Rats Diabetes Mellitus Model	*Allium sativum L*	Isnaini *et al*., 2019
11	The Effects of Ethanol Extract and Ethyl Acetate Fractionation of *Sechium edule Jacq. Swartz* on Triglyceride Levels In Male Rats With Type 2 Diabetes Mellitus	*Sechium edule Jacq*	Siahaan *et al*., 2019
12	Test Antihyperglycemia Ethanol Leaf Extract Kembang Bulan (*Tithonia diversifolia*) in Mice (*Mus musculus*) The Induced Diabetes With alloxan	*Tithonia diversifolia*	Pasaribu *et al*., 2019
13	Effectiveness of Dry Extract Mahoni Seed Consumption On Blood Sugar Level In Diabetes Mellitus Patients	*Swietenia macrophylla*	Ardiansyah *et al*., 2021

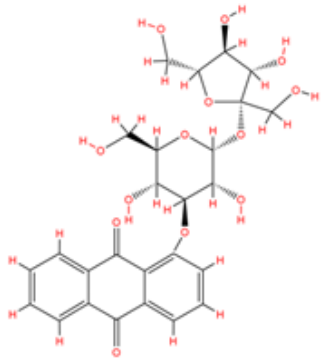
14	The supplementation effect of fruit skin extract on the fasting blood glucose and lipid profiles in male Wistar rats with diabetes mellitus and dyslipidemia	*Selenicereus undatus*	Marietta *et al*., 2020
15	Effect of Chlorella Vulgaris extract on high sucrose diet-induced diabetes in *Drosophila melanogaster*	*Chlorella vulgaris*	Salim *et al*., 2021
16	Cinnamon Extract (*Cinnamomum cassia*) Against Diabetes Mellitus	*Cinnamomum cassia*	Hartawan, 2021
17	Oral administration of arabica green coffee extract increased fasting insulin and decreased fasting blood glucose but did not decrease insulin resistance in Wistar male rat (*Rattus norvegicus*) obese with diabetes mellitus	*Coffea arabica*	Maharani *et al*., 2021
18	Valuation of anti-diabetic activity of aqueous and alcoholic extract *Citrullus colocynthis* and *Trigonella foenum graceum* in STZ induced diabetes in rats	*Citrullus colocynthis, Trigonella foenum graceum*	Sharma *et al*., 2022
19	The hypoglycemic effects of tapak liman (*Elephantopus scaber L*) plant extract on albino rat (*Rattus novergicus*) models of diabetes mellitus	*Elephantopus scaber L*	Sholikah *et al*., 2020
20	An Anti-diabetic Activity Of Simbagh Utak (*Hydnophytum formicarum*) Tuber Extract On The Blood Sugar Level of Mice (*Mus musculus*) Male Induced Alloxan	*Hydnophytum formicarium*	Purnamasari *et al*., 2022
PubMed Database			
1	Total polyphenols and anti-hyperglycemic activity of aqueous fruits extract of Abelmoschus esculentus: Modeling and optimization of extraction conditions.	*Abelmoschus esculentus*	Peter *et al*., 2021
2	Antioxidative and anti-diabetic effects of Capparis spinosa fruit extract on a high-fat diet and low-dose streptozotocin-induced type 2 diabetic rats	*Capparis spinosa*	Assadi *et al*., 2021
3	A Standardized Extract Prepared from Red Orange and Lemon Wastes Blocks High-Fat Diet-Induced Hyperglycemia and Hyperlipidemia in Mice	*Citrus limon (L.) Burm.*	Chiechio *et al*., 2021
4	Anti-hyperglycemic and anti-hyperlipidemic effects of a methanolic extract of *Debregeasia salicifolia* in Alloxan-induced diabetic albino mice	*Debregeasia salicifolia*	Khan *et al*., 2021
5	Methanol-Extract/Fractions of *Dacryodes edulis* Leaves Ameliorate Hyperglycemia and Associated Oxidative Stress in Streptozotocin-Induced Diabetic Wistar Rats	*Dacryodes edulis*	Ononamadu *et al*., 2019
6	*Paederia foetida Linn*. leaf extract: an anti-hyperlipidemic, antihyperglycaemic, and antioxidant activity	*Paederia foetida Linn*	Kumar *et al*., 2014
7	Antioxidant and Anti-hyperglycemic Effects of Ephedra foeminea Aqueous Extract in Streptozotocin-Induced Diabetic Rats	*Ephedra foeminea*	Hajleh *et al*., 2022
8	Anti-diabetic, anti-hyperlipidemic, and antioxidant properties of ethanol extract of *Grewia asiatica Linn*. bark in alloxan-induced diabetic rats	*Grewia asiatica Linn*	Khatune *et al*., 2016
9	Anti-hyperglycemic and anti-hyperlipidemia effects of the alkaloid-rich extract from barks of *Litsea glutinosa* in ob/ob mice	*Litsea glutinosa*	Zhang *et al*., 2018
10	Anti-diabetic and anti-hyperlipidemic effects of ethanolic Ferula assafoetida oleo-gum-resin extract in streptozotocin-induced diabetic Wistar rats	*ferula assa foetida* oleo-gum-resin	Latifi *et al*., 2019

11	Hypoglycemic and Anti-diabetic Effect of Pleurotus sajor-caju Aqueous Extract in Normal and Streptozotocin-Induced Diabetic Rats	*Pleurotus sajor-caju*	Ng *et al*., 2015
12	Anti-diabetic and anti-hyperlipidemic activity of Piper longum root aqueous extract in STZ induced diabetic rats	*Piper longum root*	Nabi *et al*., 2013
13	Hypoglycemic, antiglycation, and cytoprotective properties of a phenol-rich extract from waste peel of *Punica granatum L. var. Dente* di Cavallo DC2	*Punica granatum L*	Di Sotto *et al*., 2019
14	Anti-hyperglycemic and anti-hyperlipidemic effects of rhinacanthins-rich extract from *Rhinacanthus nasutus* leaves in nicotinamide-streptozotocin induced diabetic rats	*Rhinacanthus nasutus*	Shah *et al*., 2019
15	A New Italian Purple Corn Variety (Moradyn) Byproduct Extract: Antiglycative and Hypoglycemic In Vitro Activities and Preliminary Bioaccessibility Studies	*Zea mays Var purple*	Ferron *et al*., 2020
16	Anti-Hyperlipidemia, Hypoglycemic, and Hepatoprotective Impacts of Pearl Millet (*Pennisetum glaucum L*.) Grains and Their Ethanol Extract on Rats Fed a High-Fat Diet	*Pennisetum glaucum L*	Alzahrani *et al*., 2022
17	Hypoglycemic Effects in Alloxan-Induced Diabetic Rats of the Phenolic Extract from Mongolian Oak Cups Enriched in Ellagic Acid, Kaempferol and Their Derivatives	*Mongolian Oak Cups*	Yin *et al*., 2018
18	Hypoglycemic triterpenoid glycosides from *Cyclocarya paliurus* (Sweet Tea Tree)	*Cyclocarya paliurus*	Sun *et al*., 2020

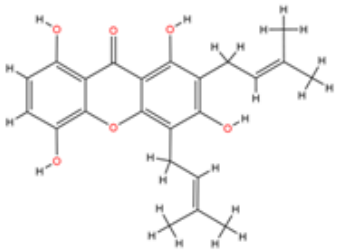
Table 2. The species with evidence for treating diabetes mellitus in Indonesia

No.	Species	Disease	Reference Code
1.	*Abelmoschus esculentus*	Diabetes	NCT03990844
2.	*Allium sativum L*	Diabetes	NCT03931434
3.	*Cinnamomum cassia*	Diabetes	NCT00479973
4.	*Citrullus colocynthis*	Diabetes	NCT02155361
5.	*Coffea arabica*	Non-Diabetes	NCT04975802, NCT04057313
6.	*Elephantopus scaber L*	-	-
7.	*Eleutherine Palmifolia (L.,)*	-	-
8.	*Hibiscus rosa-sinensis L*	-	-
9.	*Hydnophytum formicarum*	-	-
10.	*Momordica charantia*	-	-
11.	*Morinda citrifolia*	Non-Diabetes	NCT00033878, NCT01070264
12.	*Muntingia Calabura L*	-	
13.	*Musa Paradisiaca Var Kepok*	-	
14.	*Pennisetum glaucum L*	Non-Diabetes	NCT02233764
15.	*Persea americana Mill.*	-	
16.	*Punica granatum L*	Diabetes	NCT03512665
17.	*Sechium edule*	Non-Diabetes	NCT01539070

The molecular docking technique is a valuable tool in computational chemistry, enabling the simulation and analysis of atomic-level interactions between small molecules and proteins. Through this method, researchers gain insights into the behavior of small molecules within the binding sites of target proteins, advancing our understanding of fundamental biochemical processes (Bourhou *et al*., 2023).



Damnacanthol-11-O-Beta-Primeveroside



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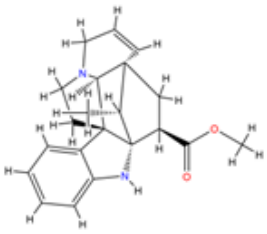
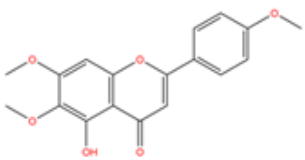
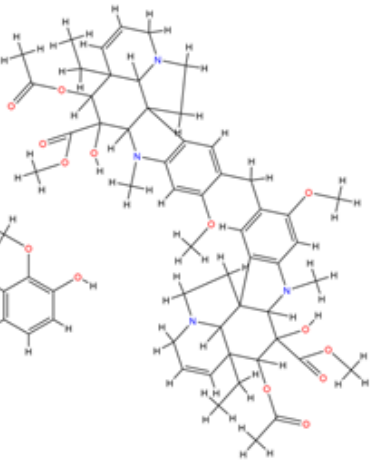


Vindolinine



Salvigenin



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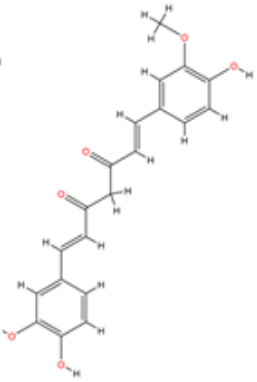

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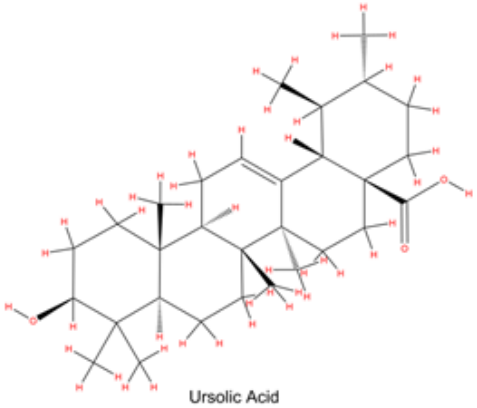
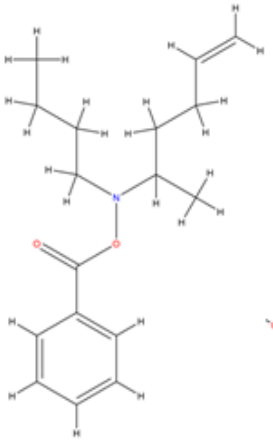
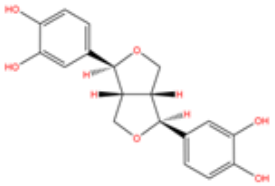


Ursolic Acid



Spatozoate



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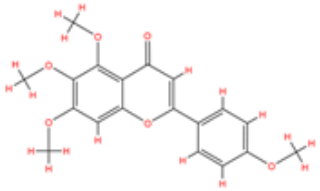
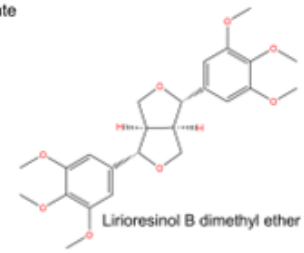
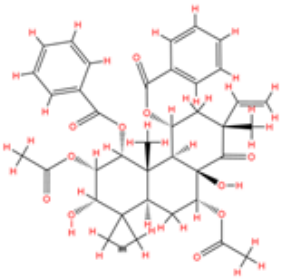


Tetramethylscutellarein



Lirioresinol B dimethyl ether



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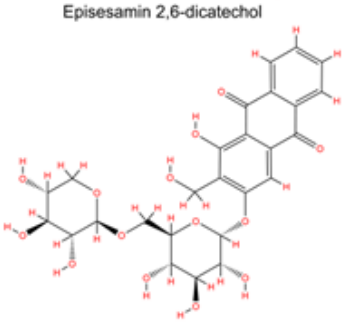
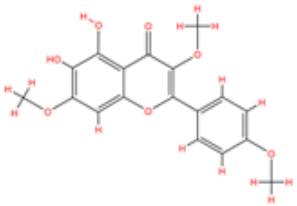
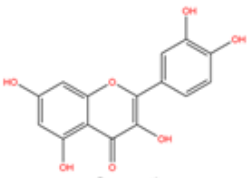


Lucidin 3-O-β-D-Primeveroside



3,7,4'-Tri-O-Methyl-Kaempferol



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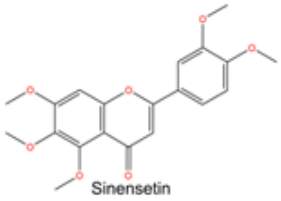
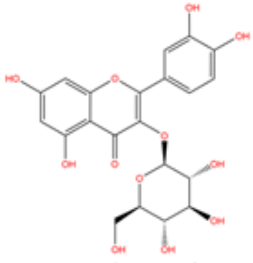
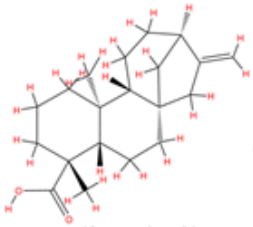


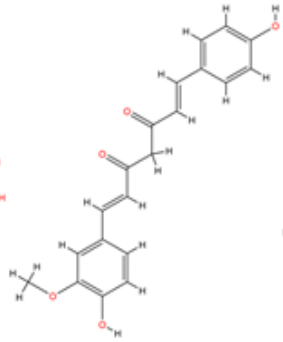
Sinensetin



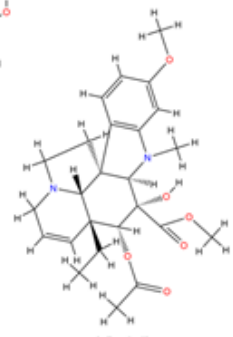
Isoquercetin



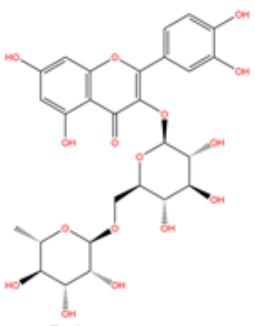
Kaurenoic acid



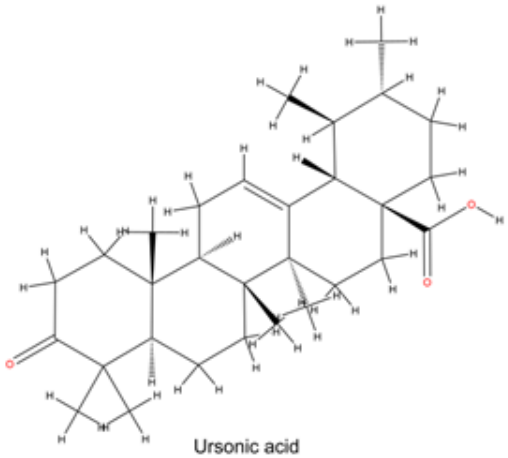
Demethoxycurcumin



Vindoline



Rutin



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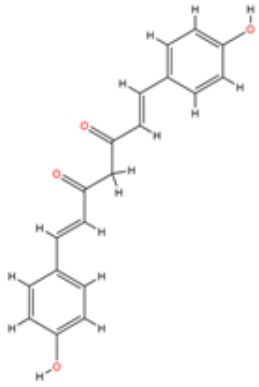

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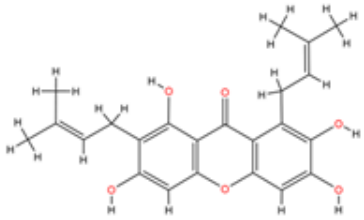
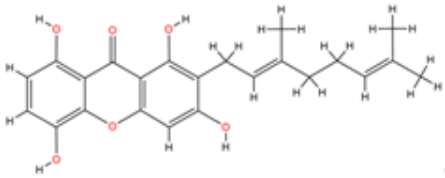
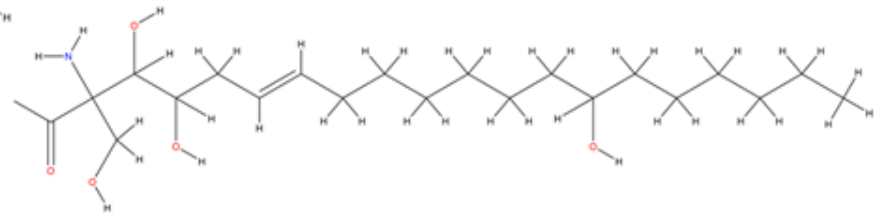


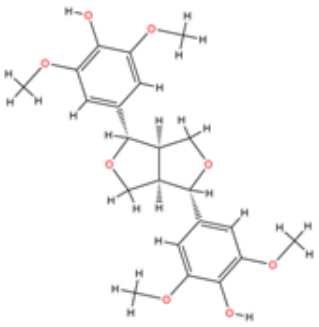
γ-mangostin



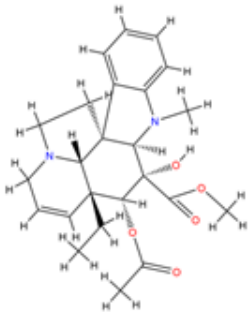
Smeathxanthone A



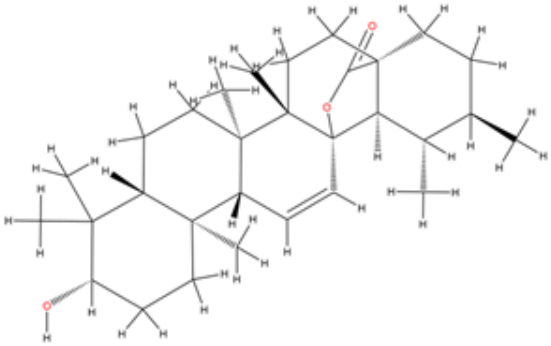
(E)-2-Amino-3,4,14-trihydroxy-2-hydroxymethyleicos-6-enoic acid



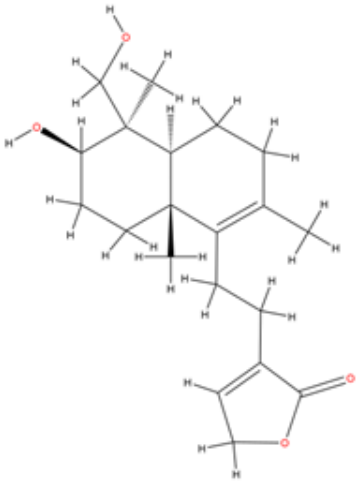
Lirioresinol B



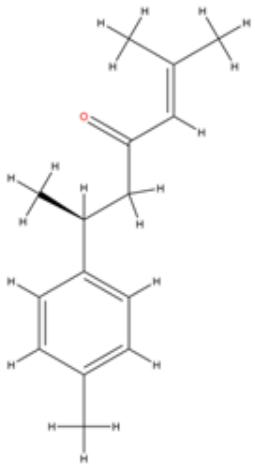
Vindolidine



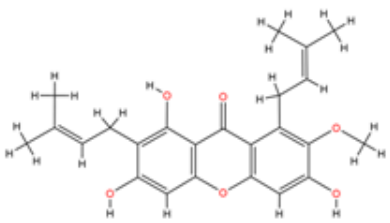
3-hydroxy-11-ursen-28,13-olide



Deoxyandrographolide



Ar-turmerone



α-mangostin

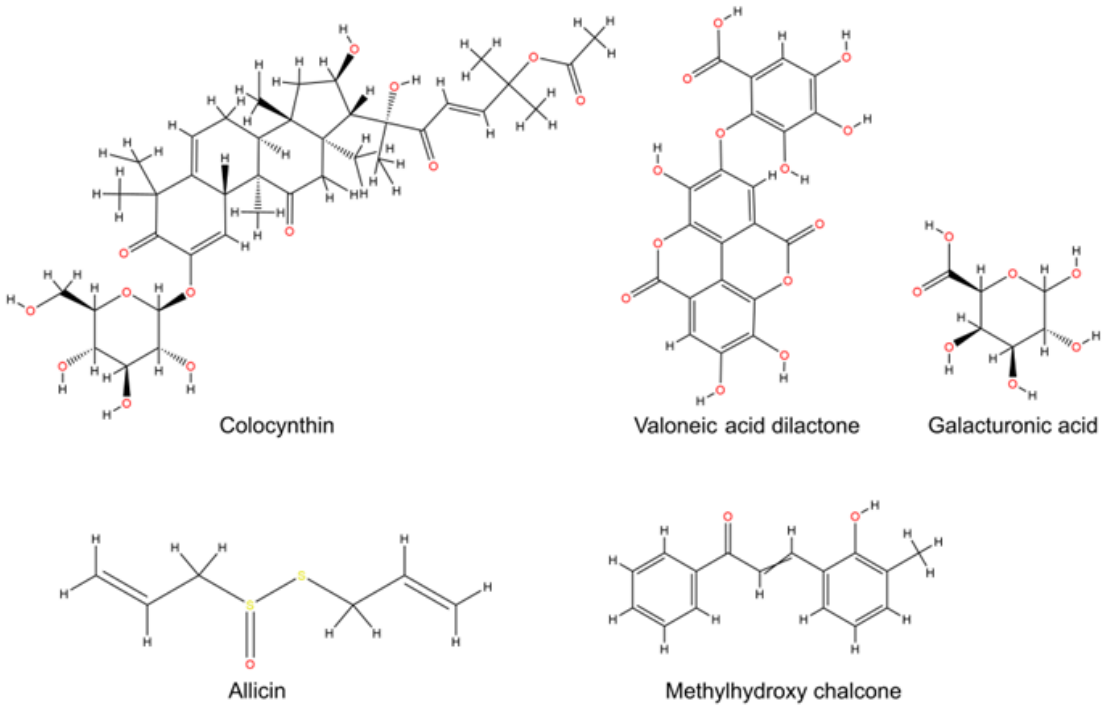


Figure 3. The anti-diabetic compounds contained in Indonesia plants used for herbal remedies

In this *in silico* docking study, the focus was on α-amylase, a pivotal protein involved in hyperglycemia. A carefully selected set of compounds, along with the Acarbose control, served as ligands for the docking simulations. Utilizing the molecular docking approach, all ligands were successfully anchored, facilitating meticulous assessment and documentation of binding scores and hydrogen bond interactions (**Table 3**).

Table 3. The docking scores and the interacting Amino Acid of the selected compounds against the α-amylase

Compound name	PubChem CID	Docking Scores (kcal/mol)	Contributing Binding Residues
Acarbose	41774	-7.615	GLY403, ASP402, ARG421, ARG398, GLY334, PRO332, ASP402
Isoquercitin	10813969	-7.716	GLY404, ASP402, GLY334, ARG398, ARG252, ASP290
Rutin	5280805	-7.361	GLY403, GLN404, GLY334, ARG421, ARG252
Quercitin	5280343	-7.083	ARG421, ASP402, ARG352, PRO332, ASP9, THR6
γ-mangostin	5464078	-6.755	ASP300, ASH197, LYS200, HIS201
α- mangostin	5281650	-6.650	ASP300, ASH197, LYS200, HIS201
Colocynthin	54584209	-5.929	THR264, TYR151, HIP305
Curcumin	969516	-5.650	GLN404, ARG252, THR6

Visual examination of the ligand-protein complexes through two-dimensional images demonstrated that all compounds efficiently occupied the active binding site within the protein's cavity. Notably, the results of these simulations revealed exceptional binding energy values for all compounds compared to the control, Acarbose (**Figure 4**). This finding indicates that the ligands exhibit a similar

binding affinity to the control, suggesting their potential as efficacious anti-hyperglycemic agents. Furthermore, the docking results corroborated the enhanced stability of the compounds during their interactions with α-amylase. This important observation supports the increased activity of these anti-diabetic compounds sourced from Indonesian plants, which have a longstanding traditional application in herbal remedies. These promising findings shed light on the prospective application of these natural compounds as groundbreaking therapies for managing hyperglycemia and diabetes, warranting further comprehensive exploration and investigation in future scientific endeavors.

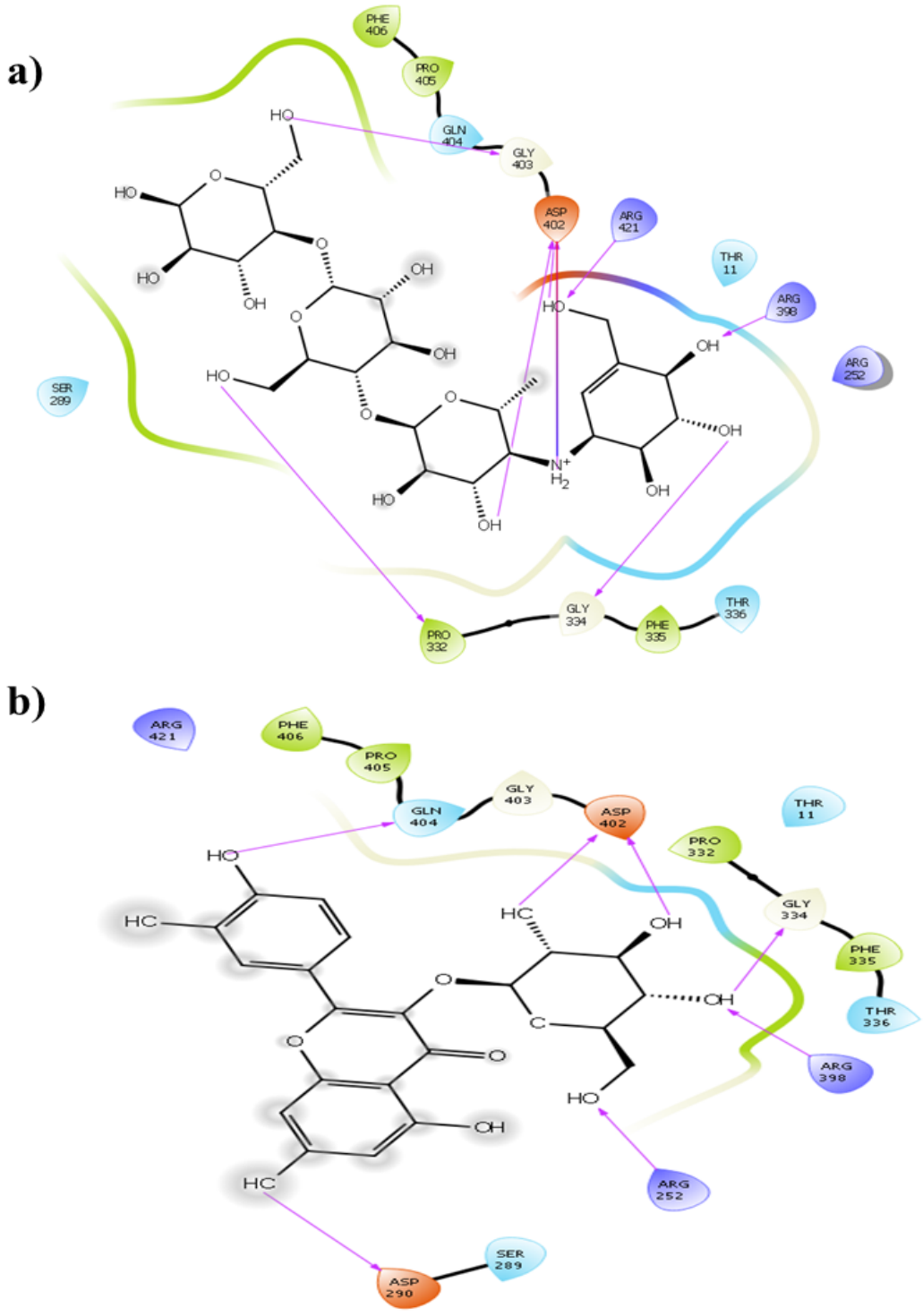


Figure 4. The 2D intermolecular interactions of the best results between (a) the control Acarbose and α-amylase, and (b) isoquercetin with α-amylase.

Conclusion

This systematic review compiles the Indonesian herbal medicine databases from PubMed, Portal Garuda and BDTOI. We obtained 20 articles in Portal Garuda and 18 in PubMed matching the inclusion and exclusion criteria of this research, and 17 species matched with BDTOI for both Portal Garuda and PubMed databases. Further, the clinical trial mapping with https://clinicaltrials.gov/ demonstrated five species have the ability for anti-diabetic such as *Abelmoschus esculentus, Allium sativum L, Cinnamomum cassia, Citrullus colocynthis*, and *Punica granatum L*. We identified over 30 active compounds in Indonesian herbal medicine for anti-diabetic treatments.

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Compliance with Ethical Standards: This article does not contain any studies involving human or animal subjects.

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