South African Journal of Botany 149 (2022) 537–558

Contents lists available at ScienceDirect

South African Journal of Botany

journal homepage: www.elsevier.com/locate/sajb

Review

A review of medicinal plants for the treatment of diabetes mellitus: The case of Indonesia

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ARTICLE INFO

Article History:
Received 4 March 2022
Revised 17 June 2022
Accepted 17 June 2022
Available online 28 June 2022

Edited by Dr K. Balkwill

Keywords:
Diabetes mellitus
Ethnopharmacology
Phytochemical
Toxicology
Traditional medicine

ABSTRACT

Indonesia is rich in biodiversity and ethnic groups, including those that use traditional medicine to treat diabetes mellitus (DM). Ethnopharmacological of antidiabetic medicinal plants is still an essential field of study to organize preclinical and clinical trials. This study presents a review of the ethnopharmacology of antidiabetic plants and their scientific information, focusing on highlighting gaps and direction for further studies. Data were obtained from online and offline sources to identify Indonesian medicinal plants used to lower blood glucose. Ethnopharmacological literature was searched from Google Scholar with keywords: ethnobotany AND medicinal plant AND diabetes AND Indonesia; an ancient book (*Cabe Puyang Warisan Nenek Moyang*), government reports on ethnopharmacological surveys, and BSc/MSc/PhD theses indexed and not indexed internationally. Subsequently, other sections regarding preclinical trials (*in vitro* and *in vivo*), phytochemical issues, clinical trials, and toxicological assessments were searched from Scopus with the relevant keywords. A total of 229 medicinal plant species belonging to 70 families and are used to treat DM were listed in this study. Among these plants, Asteraceae and *Orthosiphon aristatus* (Blume) Miq. were the most dominant plant family and species, respectively. Most of the herbal recipes were from North Sumatera (102 recipes). Leaf and boiling were the most applied plant part and mode of preparation, respectively. Furthermore, the top 10 highly cited antidiabetic medicinal plants from ethnopharmacological data were assessed in the preclinical (*in vitro* and *in vivo*), phytochemical issues, clinical trials, and toxicological tests. Pharmacological, phytochemical, clinical, and toxicological studies have been reported; meanwhile, many research opportunities can be explored, especially plants lacking scientific evidence. This study's application is expected to accelerate the drug discovery and development from natural resources to treat DM. Moreover, hopefully, medicinal plants can be one of the solutions to treat DM that is effective, safe, and sustainable.

1. Introduction

Diabetes mellitus (DM) is a chronic disease and endocrine dysfunction marked by hyperglycemic conditions and characterized by insulin deficiency, insulin resistance, or both (Ighodaro, 2018; Ebrahimpour-koujan et al., 2018; Halim and Halim, 2019; Maleki et al., 2019; Belwal et al., 2020). Long-term DM can lead to several complications, including microvascular complications, such as neuropathy, nephropathy, and retinopathy, and macrovascular complications, comprising atherosclerosis, heart attack, and peripheral blood vessel disease (Koulis et al., 2015; Ighodaro, 2018; Yeung et al., 2018). The prevalence of DM has shown an increasing number of cases at the national, regional, and global levels (Cho et al., 2018; International Diabetes Federation, 2019). The IDF reported 88 million cases in South-East Asia and predicted that the prevalence of DM will increase by 74% between 2019 – 2045 (International Diabetes Federation, 2019). Indonesia is predicted to account for 21.3 million DM cases in 2030 and is estimated to rank fourth at the global level after India, China, and the United States (Indonesian Ministry of Health, 2019). In addition to prevalence, DM has high mortality and morbidity rates, causes severe complications, and is a global economic burden (Bommer et al., 2018; Zhou and Byard, 2018).

The information above prompted scholars and health practitioners to search for more insights into these health problems by focusing on natural products as an attractive approach to prevent

Abbreviations: DM, diabetes mellitus; GLUT, glucose transporter; IDF, International Diabetes Federation; STZ, streptozotocin

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https://doi.org/10.1016/j.sajb.2022.06.042
0254-6299/

and/-or cure DM (Jugran et al., 2020; Rohman et al., 2020). Natural compounds play a fundamental role in discovering antidiabetic drug agents, *i.e.*, metformin derived from *Galega officinalis* L., that effectively manages type 2 DM (He et al., 2019). Several natural compounds control DM with various critical targets of drug action (He et al., 2019). Additionally, management of DM treatment requires a multi-key target approach to regulate glucose homeostasis in experimental models and patients (Li et al., 2018).

In general, one of the information sources about medicinal plants is an ethnopharmacology study that provides reliable information from the local community and contributes to the discovery and development of natural drugs (Nowbandegani et al., 2015; Yaseen et al., 2015; Rivera et al., 2019; Ndhlovu et al., 2021). This data can be developed from primary and secondary information sources, including ethnic communities, traditional healers, medicinal plant traders, village and religious leaders, farmers, Islamic Scriptures (Holy Qur'ân and Ahadith), ancient books, encyclopedic books, and other sources (Ceuterick et al., 2008; Roosita et al., 2008; Silalahi et al., 2015a; Sujarwo et al., 2015; El-Seedi et al., 2019; Dixit and Tiwari, 2020). Indonesia is a prospective country for developing natural drugs due to its high biodiversity and ethnic groups (Elfahmi et al., 2014; Göltenboth, 2006). The country has more than 300 ethnic groups, including Javanese, Dayaknese, Balinese, Minangnese, and many more, with their language, culture, and history of traditional medicine practices (Göltenboth, 2006; Rahayu et al., 2020a; Wasis et al., 2020).

Several ethnopharmacological studies have been conducted in Indonesia. However, despite being a multi-cultural country, the reviews of ethnopharmacological studies, especially for the treatment of DM, are lacking. Thus, the current study attempted to provide a comprehensive dataset of the existing ethnopharmacological knowledge used in DM management which considers all species used by local communities in Indonesia. The plant species may include native and introduced species. Thus, we also reported pharmacological evidence (preclinical and clinical trials), phytochemical issues, and toxicological assessments. Our assessments are expected to highlight gaps in previous studies and offer essential directions for future frameworks of developing novel phytomedicines for combating DM.

2. Materials and methods

2.1. Data sources and search strategy

Reference literature was obtained from online and offline sources, focusing on Indonesian medicinal plants used to treat DM. We used the following databases, *i.e.*, Google Scholar, Scopus, and offline sources. For ethnopharmacological data, we used both online and offline sources indexed and not indexed internationally. Online sources through Google Scholar (17th July 2021), with keywords: ethnobotany AND medicinal plant AND diabetes AND Indonesia Furthermore, we used an ancient book (*Cabe Puyang Warisan Nenek Moyang*), government reports on ethnopharmacological surveys, and BSc/MSc/PhD theses.

For scientific evidence sections, *i.e., in vitro* activities, *in vivo* studies, phytochemical issues, clinical trials, and toxicological evidences, we followed a literature search through the Scopus. We searched using the following keywords for the preclinical trials section (*in vitro* and *in vivo*): ("selected plant name species") AND (diabet* OR "diabetes mellitus" OR dm OR insulin OR glucose). For the phytochemical section, we used the same articles as used in the preclinical trials section (*in vitro* and *in vivo*). We searched using the following keywords for the clinical trials section: ("selected plant name species") AND (diabet* OR "diabetes mellitus" OR dm OR insulin OR glucose) AND (clinic* OR "clinical trials" OR "clinical studies" OR patient OR volunteer). We searched using the following keywords for the toxicological section: ("selected plant name species") AND (toxicity OR toxicology OR "adverse effect" OR "side effect"). Subsequently, the reference lists were screened using specific criteria described in Section 2.2. about study selection and analysis.

2.2. Study selection and analysis

In general, this study was divided into two main sections, *i.e.*, ethnopharmacological data and scientific evidence. A screening of published literature was initially performed, and eligible scientific studies were selected based on the abstract. Thus, we divided two eligibility criteria into ethnopharmacological data and scientific evidence. The searching process of ethnopharmacological data is presented in the flow diagram in Fig. 1. The selection of articles related to ethnopharmacological data was based on the inclusion and exclusion criteria listed below. The inclusion criteria related to ethnopharmacological data, *i.e.*, (1) original article; (2) ethnopharmacological studies of Indonesian medicinal plants related to DM; (3) the studies used English or Indonesian language (Bahasa); and (4) accepted scientific names and synonimous names plants according to the Plants of the World Online (http://www.plantsoftheworldonline.org/), International Plant Names Index (https://www.ipni.org/), or The Plant List (http://www.theplantlist.org/). The exclusion criteria for the ethnopharmacological data, *i.e.*, (1) irrelevant to lowering blood glucose (for instance, diabetic wound); (2) unclear identification of plant species; (3) least and biased information; and (4) unavailable full-text and/ or repetitive information.

Firstly, we used Publish or Perish through Google Scholar with keywords ethnobotany AND medicinal plant AND diabetes AND Indonesia. The record revealed 5536 pieces of literature. This literature was screened based on eligibility criteria. Thus, 5411 articles were excluded, and 125 articles were used in further analysis. Moreover, in another search through Google Scholar directly, we found 26 articles relevant to the eligibility criteria. An ancient book, two government reports, and ten accessible BSc/MSc/PhD theses fulfilled the eligibility criteria (Fig. 1). Subsequently, eligible literature of ethnopharmacological data was managed using Microsoft Excel 2019 software. Although ethnopharmacological articles originally reported plant names using synonyms, we tabulated accepted or synonyms names. Subsequently, the studies were classified based on poly- or monoherbal recipes and examined for their recipes, mode of preparations, dosage and frequency, family name, vernacular name, plant parts used, provinces and ethnicity.

Secondly, we selected the top 10 highly cited antidiabetic medicinal plants from ethnopharmacological data and reviewed them in the scientific evidence section. The selection of articles related to scientific evidence was based on the inclusion and exclusion criteria listed below. The inclusion related to scientific evidence, *i.e.*, (1) primary research (original article); (2) sources from reputable journals; (3) for preclinical trial sections, (a) experimental studies which carried out preclinical trials (*in vitro* or *in vivo*), and (b) studies reported antidiabetic with a mechanism of action; (4) for phytochemical sections, studies that met the eligibility requirements of both inclusion and exclusion criteria from the preclinical sections; (5) for clinical trial sections, studies reported clinical trials of antidiabetic activity of selected plants mentioned in ethnopharmacological data in this study; and (6) for toxicological sections, studies reported toxicological assessments of antidiabetic activity of selected plants mentioned in ethnopharmacological data in this study. The exclusion related to scientific evidence, *i.e.*, (1) for preclinical trial sections, (a) *in silico* studies of antidiabetic activity of selected plants, (b) *in vivo* studies which were not carried out either pre-diabetes or DM models, (c) *in vitro* or *in vivo* studies of antioxidant activity without a clear relation to pre-diabetes or DM models; (2) for phytochemical sections, (a) studies that reported not a single compound, such as extracts and fractions, (b) studies that reported unidentified compounds; (3) inadequate information or articles without full-text; and (4) studies with a similar topic but were older than other studies.

We presented scientific evidence in tables, assessed plant extracts, fractions and/ or compounds, concentrations used (*in vitro*), doses with the route of administration and duration (*in vivo*), the models used in the study, results, and mechanisms of action for preclinical

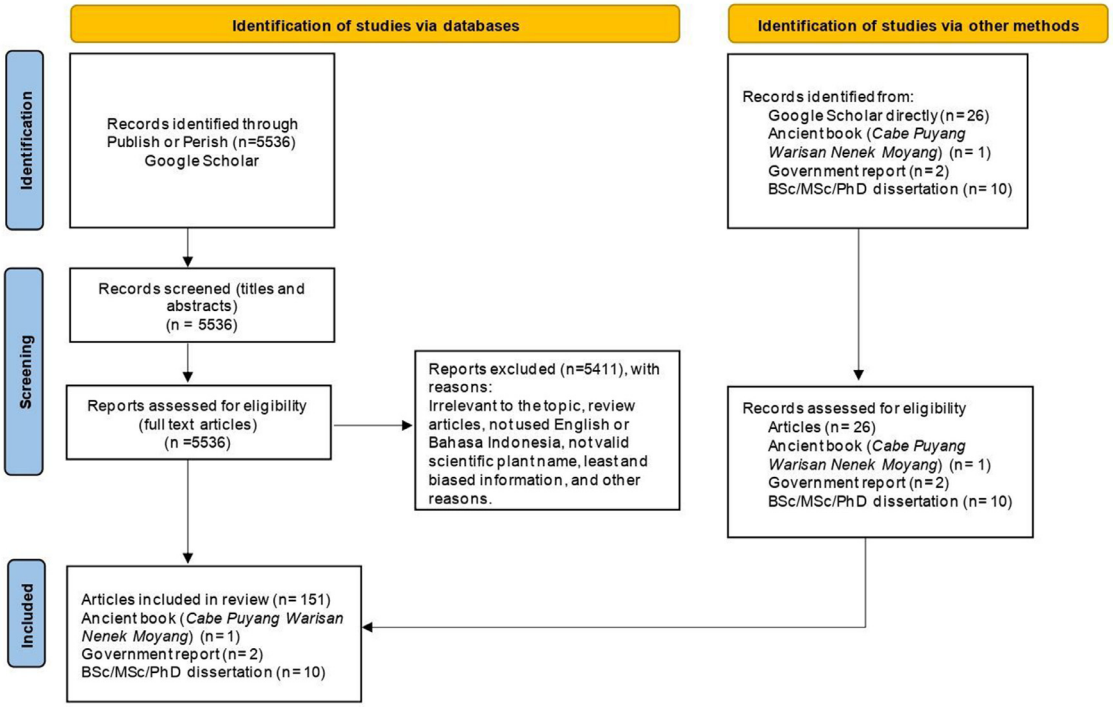

Fig. 1. A flow diagram of the search process of ethnopharmacological data.

sections. Phytochemical sections exhibited phytochemical sources, class of compounds, phytochemicals name, and chemical structure. For phytochemical compounds were listed in the PubChem and depicted using MarvinSketch. Clinical trials sections showed extract/ fraction(s) or compounds, doses and durations, participants, results, and outcomes. Moreover, toxicological sections presented extract/ fraction(s) or compounds, doses/ concentrations with the route of administration and duration, models of toxicological studies, sample sizes, and effects.

3. Results

3.1. Indonesian medicinal plants used traditionally to treat DM

The ethnopharmacological surveys revealed by poly- or mono-herbal recipes of Indonesian medicinal plants to treat DM (Appendix 1 and Appendix 2). From the abundance reports, 229 plant species belonging to 70 families were reported to treat DM. *Orthosiphon aristatus* (Blume) Miq. (cited 25 times) was the most cited in ethnopharmacological surveys, followed by nine plants, *i.e., Andrographis paniculata* (Burm.f.) Nees (cited 23 times), *Tinospora crispa* (L.) Hook.f. & Thomson (cited 18 times), *Leucaena leucocephala* (Lam.) de Wit (cited 17 times), *Physalis angulata* L. (cited 16 times), *Morinda citrifolia* L. (cited 15 times), *Syzygium polyanthum* (Wight) Walp. (cited 14 times), *Catharanthus roseus* (L.) G.Don (cited 12 times), *Syzygium cumini* (L.) Skeels (cited 12 times), and *Areca catechu* L. (cited 11 times).

The five most-cited families were Asteraceae, Fabaceae, Lamiaceae, Poaceae, and Malvaceae. In our study, Asteraceae consisted of *Ageratum conyzoides* L., *Bidens pilosa* L., *Blumea balsamifera* (L.) DC., *Clibadium surinamense* L., *Eupatorium odoratum* L. (synonym name: *Chromolaena odorata* (L.) R.M.King & H.Rob.), *Eupatorium inulifolium* Kunth, *Gymnanthemum amygdalinum* (Delile) Sch.Bip., *Gynura procumbens* Merr., *Helianthus annuus* L., *Smallanthus sonchifolius* (Poepp.) H.Rob., *Spilanthes iabadicensis* A.H.Moore (synonym name: *Acmella uliginosa* (Sw.) Cass.), Spilanthes ocymifolia A.H. Moore (synonym name: *Acmella alba* (L'Hér.) R.K.Jansen), *Taraxacum officinale* F.H. Wigg. (synonym name: *Taraxacum* sect. *Taraxacum* F.H.Wigg.), *Tithonia diversifolia* (Hemsl.) A.Gray, and *Vernonia. Amygdalina* Delile (accepted name: *G. amygdalinum*).

The identified species of Fabaceae included *Adenanthera pavonina* L. *Archidendron pauciflorum* (Benth.) I.C.Nielsen, *Pithecellobium jiringa* (Jack) Prain (synonym name: *Archidendron jiringa* (Jack) I.C.Nielsen), *Caesalpinia bonduc* L. (synonym name: *Guilandia bonduc* L.), *Erythrina subumbrans* (Hassk.) Merr., *Erythrina variegata* L., *Glycine* max (L.) Merr. L. *leucocephala, Mimosa pigra* L., *Parkia speciosa* Haskk., *Pterocarpus indicus* Willd., *Senna alata* (L.) Roxb., *Senna siamea* (Lam.) H.S. Irwin & Barneby, and *Vigna unguiculata* (L.) Walp. The members of Lamiaceae used in the DM treatment consisted of *Coleus amboinicus* Lour., *Clerodendrum indicum* (L.) Kuntze, *Clerodendrum japonicum* (Thunb.) Sweet, *Coleus scutellarioides* (L.) Benth.**,** *Hyptis capitata* Jacq., *Leucas lavandulifolia* Sm., *Mentha aquatica* L., *Ocimum sanctum* L. (synonym name: *Ocimum tenuiflorum* L.), *O. aristatus, Tectona grandis* L.f., *Vitex pinnata* L., and *Vitex trifolia* L.

Poaceae family to treat DM consisted of *Bambusa affinis* Munro, *Bambusa horsfieldii* Munro, *Bambusa vulgaris* Schrad ex J.C.Wendl., *Cymbopogon citratus* (DC.) Stapf, *Eleusine indica* (L.) Gaertn., *Imperata cylindrica* (L.) P.Beauv, *Oryza sativa* L., *Oryza sativa* L. var *glutinosa*, Saccharum offinarum L., *Saccharum spontaneum* L., *Schizostachyum blumei* Nees, and *Zea mays* L. The members of Malvaceae contained *Ceiba pentandra* (L.) Gaertn., *Guazuma ulmifolia* Lam., *Hibiscus sabdariffa* L., *Kleinhovia hospita* L., *Pterospermum celebicum* Miq., *Pterospermum javanicum* Jungh., *Sida rhombifolia* L., *Theobroma cacao* L., and *Urena lobata* L.

Our literature evaluations showed that local communities used 17 plant parts including leaf, fruit, root, seed, bark, stem, rhizome, whole plant, flower, tuber, bulb, fruit peel, resin, corm, spines, shoot, and peduncle; leaf was the most preferred plant part for DM treatment (Fig. 2). The leaf is advantageous and has a low risk for sustainable production of herbal products due to the non-threatened state of the plant species; moreover, local communities prefer limited destruction to the plants (Chen et al., 2016; Cock and Van Vuuren, 2020). However, approximately 14.21% of ethnopharmacological reports have not indicated the plant parts used. Thus, we could not identify

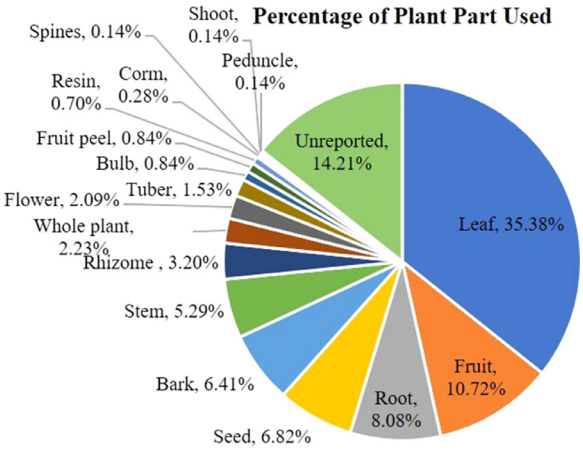

Fig. 2. Plant parts used in ethnopharmacological studies of DM treatment in Indonesia.

all the plant parts used in the selected studies. Thus, further ethnopharmacological surveys are suggested to clarify this information.

Local communities used numerous modes of preparations to prepare medicinal plant recipes. The modes included boiling, decocting, treating as a raw material plant form, brewing, pounding, juicing, roasting, marinating, powdering, water extraction, eaten as vegetable, tapping, dipping, fermenting, chip formation, rubbing, mixing in wine, and grating. Of those modes of preparations, most medicinal plant preparations were boiled and decocted. The dominance of boiling and decoction was due to the utilization of plants for nutritional and medicinal purposes (Shankar et al., 2012). However, more than 50% of ethnopharmacological reports have not reported medicinal plant preparations. The mode of preparations is essential to decide the planning of extraction methods in the laboratory and pharmaceutical industry. In addition, most medicinal plants are used internally via the oral route. However, numerous ethnopharmacological surveys did not report the mode of preparations and route, used to administer medicinal plants. Thus, further surveys are required. Important information, such as plant material conditions, including the use of fresh or dried plants (Donno et al., 2016), plant maturity (Figueroa-Pérez et al., 2018), duration of preparation (Drinkwater et al., 2015), and influence of phytochemical compounds was also not well explored. In addition, other information, including the dosage and duration of plant's uses, was poorly defined. Thus, further ethnopharmacological surveys can be prepared for preclinical studies. Further, several ethnopharmacological reports lacked information on the plant parts used and preparation modes.

Ethnopharmacological studies of antidiabetic medicinal plants have been conducted in five major islands in Indonesia, including Sumatera, Java, Kalimantan, Sulawesi, and Papua, which spread out in 31 provinces (Fig. 3). Eleven provinces reported the highest numbers of herbal recipes, *i.e.*, North Sumatera (102 recipes), West Java (89 recipes), East Java (55 recipes), Central Sulawesi (49 recipes), Central Kalimantan (38 recipes), Central Java (35 recipes), Southeast Sulawesi (20 recipes), West Nusa Tenggara (16 recipes), Aceh (15 recipes), East Nusa Tenggara (15 recipes), and West Kalimantan (15 recipes). Furthermore, South Sulawesi (11 recipes), South Sumatera (10 recipes), West Sumatera (9 recipes), Bali (8 recipes), North Sulawesi (7 recipes), Riau (6 recipes), Special Region of Yogyakarta and Maluku (5 recipes), Banten and East Kalimantan (3 recipes), Bengkulu, Gorontalo, West Sulawesi, North Maluku, and Papua (2 recipes), Jambi, Bangka Belitung Archipelago, Lampung, South Kalimantan, and North Kalimantan (1 recipe). Meanwhile, 1 recipe was reported from the Lesser Sunda Islands, 1 recipe from 11 villages around Indonesia, and 2 from Kalimantan Island. On the other hand, numerous ethnopharmacological reports did not provide survey regions, *i.e.*, 29 herbal recipes, especially those from ancient books and government reports. Moreover, three provinces had no recipes, including Riau Archipelago, Jakarta, and West Papua. The lack of ethnopharmacological reports in several regions may be due to the inadequate number of surveys, poor documentation, unpublished data, and other reasons; thus, the development of detailed medicinal plant databases are encouraged (Khoomrung et al., 2017).

3.2. Scientific evidence of selected Indonesian antidiabetic plants

The top 10 highly cited antidiabetic medicinal plants from ethnopharmacological data were evaluated based on scientific evidence, including preclinical trials (*in vitro* or *in vivo*), phytochemicals, clinical trials, and toxicological assessments. These plant species were *O. aristatus, A. paniculata, T. crispa, L. leucocephala, P. angulata, M. citrifolia, S. polyanthum, C. roseus, S. cumini*, and *A. catechu*.

3.2.1. Preclinical trials (in vitro or in vivo)

Ethnopharmacological studies are mainly accomplished disease models through *in vitro* or *in vivo* approaches. *In vitro* studies using various models, such as enzymes, cell cultures, and tissues. The latter is sufficiently simple, quick, and cost-effective approaches to underlying molecular mechanisms of diseases (Andrade et al., 2020). Preclinical trials of selected Indonesian antidiabetic plants are shown in Table 1. All of 10 selected plants have been investigated through *in vitro* studies. Seven species were found to have inhibition activities of both α-amylase and α-glucosidase, namely *O. aristatus, A. paniculata, T. crispa, M. citrifolia, S. polyanthum, C. roseus*, and *S. cumini*; two species were found to only have an inhibition activity of α-amylase, namely L. *leucocephala* and *P. angulata*. Four selected plants also have an activity to inhibit PTP1B, including *O. stamineus, A.* paniculata, C. *roseus*, and *S. cumini*. Additionally, the inhibition activities of dipeptidyl peptidase-IV activity were found in *A. paniculata, T. crispa, P. angulata, S. polyanthum*, and *S. cumini*. Furthermore, *S. cumini* exhibited an antiglycation activity. Other mechanisms of diabetes that have been studied through *in vitro*, include inhibition of lipase, glucose uptake, and antioxidant; and inhibition of sucrase and maltase.

In vitro evaluation of antidiabetic properties has been acquired using cellular models of both cell lines and representative organs related to the physiopathology of diabetes. The mechanism of action to enhance glucose uptake using cell lines involved 3T3-L1 cells (*O. stamineus, A. paniculata, T. crispa*, and *S. cumini*), myoblast C2C12 cells (*A. paniculata, T. crispa*, and *C. roseus*), LO-2 cells (*P. angulata*), and HepG2 cells (*M. citrifolia*). Additionally, other mechanisms of action of 10 selected plants include stimulating insulin-producing (PANC-1 cells), antiapoptotic (H9c2 cardiomyocytes cells and MES-13 cells), inhibiting the activator protein-1 pathway (mesangial cells), improving insulin sensitivity (IR-HepG2 cells), regulating insulinotropic activity (HIT-T15 cells and BRIN-BD11 cells), stimulating insulin release (RIN-5F cells), regulating *peroxisome* proliferator-activated receptor (Cos7 cells), and regulating intestinal glucose transport (Caco-2 cells), Furthermore, representative organs to explore some mechanisms of action, such as to enhance glucose uptake (primary hippocampal cultures), to stimulate insulin release (islet pancreatic), to stimulate adipogenesis and enhance glucose uptake (preadipocytes), to inhibit glucose absorption (jejenum), and to regulate gluconeogenesis (primary hepatocytes).

In addition to *in vitro* studies, preclinical trials also require *in vivo* studies. *In vivo* studies are essential to set effective dosages, dose on the therapeutic index ranges, time of experiments, type of diabetic inductions, type of plants extracts, and active constituents (Andrade et al., 2020; Ardalani et al., 2021). Ten selected plants revealed that 1 species have no *in vivo* evidence, *i.e.*, L. *leucocephala*. Meanwhile, other species have been reviewed at least in one *in vivo* study using animal model of diabetes. The diabetes model is mostly induced in animal models through intraperitoneal administration of

Fig. 3. Locations of the surveyed provinces (blue sign), as modified from Google Maps. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

streptozotocin (STZ), diabetogenic inducers agents. STZ induces the destruction of β cells through glucose transporter (GLUT)−2 with several mechanisms, including oxidative stress, apoptosis, and mitochondrial dysfunction Goyal et al., 2016; Nahdi et al., 2017; Andrade et al., 2020).

Several antidiabetic mechanisms of action have been studied through *in vivo* approach, including interaction of peptides (*O. stamineus*), regulation of glucose metabolisms (*O. stamineus, T. crispa, M. citrifolia, C. roseus*, and *S. cumini*), regulation lipid metabolism (*T. crispa* and *C. roseus*), enhancement of glycogen synthesis (*S. cumini*), enhancement of glucose uptakes (*O. stamineus, A. paniculata, S. polyanthum*, and *S. cumini*), reduction of glucose absorptions (*O. stamineus*), anti-inflammation (*A. paniculata* and *C. roseus*), stimulation of insulin production (*A. paniculata*), stimulation of insulin release (*T. crispa* and *S. cumini*), inhibition of indoleamine 2, 3-dioxygenase related to retina (*A. paniculata*), antioxidant (*A. paniculata, P. angulata, M. citrifolia*, and *C. roseus*),antiapoptotic (*A. paniculata*), antiangiogenetic (*A. paniculata*), maintain immune systems (*A. paniculata*) inhibition of glycolytic and gluconeogenic (*A. paniculata*), improvement of endothelial dysfunction (*A. paniculata*), regulation lipogenesis (*M. citrifolia*), regulation of AGEs pathway (*S. polyanthum*), regulation of glucose transport (*C. roseus*), and protection of β cells (*S. cumini*).

3.2.2. Phytochemicals

Phytochemical fields are crucial steps in finding the structure of chemical molecules in traditional medicines (Tanaka and Kashiwada, 2021). These steps are performed based on the information obtained by ethnopharmacological surveys, which contributed to identifying lead compounds for drug discovery and development (Hao and Xiao, 2020; Tanaka and Kashiwada, 2021). Thus, the phytochemistry of selected medicinal plants was also assessed in this study. Seven species that explored the phytochemicals against DM were *O. aristatus, A. paniculata, T. crispa, P. angulata, M. citrifolia, C. roseus*, and *S. cumini*. Many compounds detected in these selected plants were terpenes (pimarane diterpenes, diterpenoid lactones, diterpenes, diterpenoid glycosides, and triterpenoid saponins), flavonoids, steroids, coumarins, indole alkaloids, and phenolics. Terpenoids were the dominant appearance among the class of compounds. Terpenoids have several mechanisms as antidiabetic, such as α-amylase and α-glucosidase inhibitors, aldose reductase inhibitors, PTP1B inhibitors, glycogen phosphorylase inhibitors, insulin mimetic actions, and oxidative stress inhibitors (Nazaruk and Borzym-Kluczyk, 2015; Panigrahy et al., 2021). Moreover, terpenoids were also impaired in diabetic complications involving diabetic neuropathy, nephropathy, retinopathy, or wound healing by inhibiting several pathways (Putta et al., 2016). The antidiabetic activities of terpenes were due to the highest number of hydrogen bonds and hydrophobic interactions (Panigrahy et al., 2021).

3.2.3. Clinical trials

An abundance usage of medicinal plants has been attributed to possessing antidiabetic agents. Furthermore, most of the world's population depend on herbal medicines in primary health care (Barzkar et al., 2020; Naveen et al., 2021). Herbal medicines are one of the alternatives to treat DM in several cultures around the world (Naveen et al., 2021). Thus, clinical trials are essential steps in developing natural remedies, especially in health care. In the current study, 5 of 10 selected plants were tested at the clinicals trials level, *i.e., A. paniculata, T. crispa, M. citrifolia, S. polyanthum*, and *S. cumini.* (Table 3). The previous clinical trials showed various dosage forms (capsules, tablets, juices, powders, teas, decoctions, and other dosage forms), and single or combinations with other plants. Moreover, the clinical trials involved participants from a healthy subject and DM patients with outcomes to improve glucose, lipid, metabolic, and insulin profile, to reduce inflammation and oxidative stress, and to modulate enzymes related to the bioactivity of insulin.

3.2.4. Toxicological assessments

The utilization of plants to treat diseases is widely used in many countries, and it is believed that medicinal plants have fewer side effects and are safer than synthetic drugs (Kharchoufa et al., 2018; Bouyahya et al., 2021). These perceptions are untrue and misleading. Medicinal plants can produce adverse reactions involving teratogenicity, carcinogenicity, and even death (Kharchoufa et al., 2018). Some previous studies were also revealed the interaction between herbals-drugs, herbals-herbals, or herbals-foods (Bouyahya et al., 2021). Thus, toxicological information of medicinal plants is important to be assessed. In general, toxicity tests are divided into two approaches, *i.e.*, general toxicity and specific toxicity (Subramanian et al., 2018). General toxicity assesses gross behavior and lethal dose 50 and is divided into several test types, including acute subacute, subchronic, and chronic toxicity testing (Subramanian et al., 2018). Meanwhile, some specific toxicity studies, include carcinogenicity, prenatal development toxicity, reproduction toxicity, genotoxicity, mutagenicity, and others (Subramanian et al., 2018; Rocha et al., 2019). In this study, selected plants were assessed the toxicological tests, except *T. crispa* and *P. angulata* (Table 4).

4. Discussion

Diabetes mellitus is a severe metabolic disorder that can promote various complications and reduce the quality of life of diabetic

Table 1
Preclinical screening (*in vitro* or *in vivo*) of selected Indonesian antidiabetic plants.

Family/Species	Extract/fraction(s) or compounds, dose/ concentration with the route of administration and duration	Model/sample size *In vitro*	*In vivo*	Results	Mechanisms of action	References
Lamiaceae/*Orthosiphon aristatus* (Blume) Miq.	Water extracts of leaves (0.1/100 g/kg BW), vehicle, and glibenclamide (0.6 mg/kg BW) (p.o), once daily for 14 days (non-pregnant) and 10 days (pregnant)	–	STZ (30 mg/kg BW, i.p); female Sprague-Dawley rats/ n = 6	↑ FBG, insulin, ghrelin, GLP-1 ↓ TC	Interacting with peptides	[1]
	Pimarane diterpene (5 and 10 μM), DMSO (10 μM), and insulin (100 nM)	3T3-L1 cells	–	↑ glucose uptake	Enhancing glucose uptake and inhibiting PTP1B activity	[2]
	Pimarane diterpene (4–100 μM) and ursolic acid	PTP1B assay	–	↓ PTP1B		
	Methanolic extracts of roots (200, 400, and 800 mg/kg BW), 1% gum acacia, and glibenclamide (600 μg/kg BW) (p.o) for 4 weeks	–	STZ (65 mg/kg BW, i.p) and nicotinamide (120 mg/kg BW, i.p); male Wistar rats/ n = 6	↑ insulin, glycogen, G-6-PD ↓ glucose, G-6-P	Increasing glucose metabolism	[3]
	Fraction of chloroform extracts of leaves (0.5 and 1.0 g/kg BW), saline, and metformin (500 mg/kg BW) (p.o), twice daily for 14 days	–	STZ (65 mg/kg BW, i.p); female Sprague-Dawley rats/ n = 6	↑ glucose uptake ↓ glucose, glucose absorption	Enhancing glucose uptake and inhibiting glucose absorption	[4]
	Ethanolic extracts of leaves (1.95–62.5 mg/ml), isolated sinensetin (0.3125–2.5 mg/ml), and acarbose (1.25–10 mg/ml)	α-amylase and α-glucosidase assays	–	↓ α-amylase, α-glucosidase	Inhibiting absorption of glucose at the intestine	[5]
Acanthaceae/*Andrographis paniculata* (Burm.f.) Nees	Andrographolide (20 μM) and vehicle	Primary hippocampal cultures from female Sprague-Dawley rats	–	↑ [3H]–2-deoxyglucose uptake, GLUT-3, GLUT-4, AMPK, Pfk 1, hexokinase, ATP, ATP/ADP, glycolytic rate ↓ pentose phosphate	Enhancing glucose uptake through GLUT-3 and GLUT-4 and promoting glucose metabolism through the AMPK pathway	[6]
	Bound and free phenolic extracts of leaves (50 and 100 mg/kg BW), distilled water, and glibenclamide (5 mg/kg BW), p.o for 21 days	–	Alloxan (150 mg/kg BW, i.p); male Wistar rats/ n = 6	↑ insulin, HDL, SOD, CAT, GPx, total thiol, hexokinase ↓ FBG, TC, TG, MDA, G-6-P, IL-6, TNF-α	Oxidative phosphorylation, anti-inflammation	[7]
	Ethanolic extracts of leaves (20 μl)	Lipase assay, α-amylase assay, glucose uptake assay	–	↑ glucose uptake ↓ α-amylase, lipase	Inhibiting absorption of glucose at the intestine and enhancing glucose uptake	[8]
	Andrographolide (50 mg/kg BW), saline, and liraglutide (180 μg/kg BW), p.o for 40 days	-	STZ (150 mg/kg BW, i.p); male Kunming mice/ n = 6	↑ insulin, islet cell ↓ glucose, HOMA-B	Stimulating insulin-producing through PDX-1 pathway	[9]
	Andrographolide (1.25, 2.5, and 5.0 μM) and DMSO	PANC-1 cells	–	↑ PDX-1		
	Ethanolic extracts of leaves (50 μl) and acarbose	α-amylase, α-glucosidase assays	–	↓ α-amylase, α-glucosidase	Inhibiting absorption of glucose at the intestine	[10]
	Andrographolide (1.5 and 4.5 mg/kg BW) and vehicle, for 2 months	–	STZ (35 mg/kg BW, i.p); Wistar rats/ n = 10	↑ GSH ↓ glucose, protein carbonyl, TBARS, TRP, KYN, KYNA, 3HKYN, indoleamine 2, 3-dioxygenase	Inhibiting indoleamine 2, 3-dioxygenase related to retina	[11]
	Ethanolic extracts of plant materials (0.4%), andrographolide (0.1%), 14-deoxy-11,12-didehydroandrographolide (0.05%), and vehicle, for 16 weeks	-	HFD; male C57BL/6JNarl mice/ n = 6–7	↑ insulin, IRS-1, GLUT-4, AKT ↓ glucose, HOMA-IR, TNF-α, IL-6, leptin, adiponektin	Enhancing glucose uptake through insulin signaling pathway and anti-inflammation	[12]
	Ethanolic extracts (100 μg/ml), andrographolide (20 μM), 14-deoxy-11,12-didehydroandrographolide (20 μM), and insulin (1 μg/ml)	3T3-L1 cells	–	↑glucose uptake, IRS-1, GLUT-4, AKT		

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Table 1 (*Continued*)

Family/Species	Extract/fraction(s) or compounds, dose/ concentration with the route of administration and duration	Model/sample size *In vitro*	*In vivo*	Results	Mechanisms of action	References
	Andrographolide (150 mg/kg BW) and vehicle, p.o for 8 weeks	–	C57BL/6 J mice/ n = 12	↑ Tlr2, Nrf2, CAT, Sod1, Bacteroidetes/Firmicutes, Simpson's diversity, Muc2, ↓ glucose, HOMA-IR, LPS, LBP, TNF-α, IL-6	Enhancing intestinal barrier function and enhancing microbial composition	[13]
	Andrographolide (2.5 and 5 μM) and vehicle	Caco-2 cells	–	↑ ZO-1/GAPDH, Ocln, Occludin/GAPDH, ZO-1		
	Andrographolide (1, 10, and 20 mg/kg BW) and vehicle, i.g for 12 weeks	–	STZ (50 mg/kg BW, i.p); C57/BL6J mice	↑ SOD ↓ fibrosis markers (fibrosis area, collagen I, collagen III, TGF-β, fibronectin), cardiac hypertrophy (cross-sectional area, heart weight/tibial length, ANP, BNP) NF-κB pathway (ICAM-1, VCAM-1, IL-6, IL-1β, TNF-α), MDA, 4-HNE, Nox2, Nox4, p47^{phox}, Nrf2, HO-1, Bax/Bcl-2	Antioxidant, antiapoptotic, and anti-inflammation	[14]
	Andrographolide	H9c2 cardiomyocytes cells	–	↓ ANP, BNP, apoptotic cell, Bax/Bcl-2		
	Hydro-methanolic extracts of leaves (50, 100, and 200 mg/kg BW), andrographolide (15, 30, and 60 mg/kg BW) vehicle, and piracetam (100 mg/kg BW), p.o for 10 days	–	STZ (65 mg/kg BW, i.p); male Charles Foster rats/ n = 6	↑ insulin, SOD, CAT ↓ glucose, LPO, acetylcholinesterase activity	Antioxidants related to brain function	[15]
	Ethanolic extracts of herbs and sitagliptin (0.2, 0.4, 0.8, 1.6, and 3.2 μg/ml)	DPP-IV assay	–	↓ DPP-IV	Inhibiting DPP-IV activity	[16]
	Andrographolide (10 mg/kg BW) and vehicle, i.p for 1 month	–	STZ (55 mg/kg BW, i.p); C57BL/6 mice/ n = 10	↓ retinal vessel, blood-retinal barrier, VEGF, IL-1β, IL-6, TNF-α, phospho-P65, phospho-IκB, phospho-IKK, Egr-1, tissue factor, serpine1	Inhibiting angiogenesis and inflammation through VEGF, NF-κB, Egr pathways related to diabetic retinopathy	[17]
	Andrographolide (5 μM)	Mesangial cells	–	↓ cell proliferation, fibronectin, phosphorylated c-jun, AP-1	Inhibiting the AP-1 pathway	[18]
	Andrographolide (50, 100, and150 mg/kg BW) and vehicle, p.o for 4 weeks	–	NOD mice and ICR mice	↑ GATA3 ↓ insulitis, IFN-γ, IL-2, IL-10, TGF-β, IL-17, T-bet, ROR-γt	Maintaining Th1/Th2/ Th17 homeostasis	[19]
	Water and methanolic extracts of aerial parts (25 μg/ml)	PTP-1B assay	–	↓ PTP-1B activity	Inhibiting PTP-1B pathway	[20]
	Andrographolide (1, 2, 5, and 10 μg/ml), vehicle, and insulin (10 μM)	3T3-L1 cells	–	↑ glucose uptake, IRS-1, PI3K ↓ TNF-α, IL-6, iNOS, SOCS3, MCP-1	Enhancing glucose uptake through IRS-1, PI3K, and downstream signaling cascades	[21]
	Andrographolide and 14-deoxy-11,12- didehydroandrographolide (1, 10, and 20 μM)	MES-13 cells	–	↓ caspase-3, TGF-β, PAI-1	Inhibiting apoptosis related to nephropathy diabetes	[22]
	Ethanolic extracts of aerial parts (250, 500, and 1000 mg/kg BW), andrographolide (10 mg/kg BW), distilled water (4 ml/kg BW), and metformin (500 mg/kg BW), p.o for 21 days	–	Nicotinamide (180 mg/kg BW, i.p) and STZ (45 mg/kg BW, i.p), female Sprague-Dawley rats/ n = 6	↑ glucokinase, hexokinase, LDH. G-6-PDH ↓ FBG, TC, TG, FFA, G-6-P	Inhibiting glycolytic and gluconeogenic, and promoting lipogenic	[23]
	Aqueous extracts of leaves (400 mg/kg BW) and vehicle, p.o for 30 days	–	STZ (45 mg/kg BW, i.p), female Wistar rats/ n = 10	↑ SOD, CAT, GSH, relaxation of endothelial	Repairing endothelial dysfunction	[24]
	Andrographolide (1.0–6.6 μmol/L)	Myoblast C2C12 cells	–	↑ activation of α_{1A}-adrenoceptor ↓ PLC, PKC	Enhancing glucose uptake through the PLC-PKC pathway	[25]

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Menispermaceae/*Tinospora crispa* (L.) Hook.f. & Thomson	Tinocrisposide from *T. crispa* (6.25, 12.5, 25.0, and 50.0 μg/ml), DMEM, and insulin (1 μg/ml)	3T3-L1 cells	–	↑ adipocyte differentiation	Stimulating adipocyte differentiation	[26]
	Methanolic extracts of stems (12, 25, 50, and 100 μg/ml), DMEM, and rosiglitazone maleate (100 μg/ml)	IR-HepG2 cells	–	↑ IR, Akt, GLUT-4	Improving the insulin sensitivity	[27]
	Borapetoside E (20 and 40 mg/kg BW) (i.p), 1.5% DMSO (i.p), and metformin (200 mg/kg BW) (i.g), twice a day for 2.5 day	–	HFD and 10% fructose (p.o); male C57BL/6 J mice/ n = 6	↑ insulin sensitivity index, Akt, GSK3β, GLUT-2 ↓ glucose, TG, LDL, TC, ALT, AST, creatinine, creatinine kinase, SREBP-1	Regulating glucose and lipid metabolism	[28]
	Ethanolic extracts of stems and sitagliptin (0.2, 0.4, 0.8, 1.6, and 3.2 μg/ml)	DPP-IV assay	–	↓ DPP-IV	Inhibiting DPP-IV activity	[16]
	Borapetoside C (0.5–0.8 mg/ml), DMSO, and acarbose	α-amylase and α-glucosidase assays	–	↓ α-amylase, α-glucosidase	Inhibiting absorption of glucose at the intestine	[29]
	Borapetol (1 mg/kg BW) and water (p.o) for 7 days	–	Male Wistar and Goto-kakizaki rats/n = 5	↑ insulin ↓ glucose	Stimulating insulin release	[30]
	Borapetol (0.1, 1.0, 10 μg/ml) and vehicle	Islet pancreatic from male Wistar and Goto-kakizaki rats	–	↑ insulin release		
	Borapetoside A (10^{-9}, 10^{-8}, 10^{-7}, 10^{-6}, and 10^{-5} mol/l), vehicle, and metformin (100 μM)	C2C12 cells and Hep3B cells	–	↑ glycogen	Regulating insulin-dependent and insulin-independent pathways	[31]
	Borapetoside A (0.1, 0.3, 1, 3, and 10 mg/kg BW), vehicle, and metformin (300 mg/kg BW) (i.p), twice a day for 7 days	–	STZ (250 mg/kg BW, i.p) and HFD and fructose-induced (p.o); male ICR mice/ n = 6	↑ glycogen, insulin, GLUT-2, Akt, IR, AS-160 ↓ glucose		
	Water extracts of stems (0.1 mg/ml) and buffer	HIT-T15 cells	–	↑ Ca^{2+}-uptake ↓ Ca^{2+}-efflux	Regulating insulinotropic activity through β-cell Ca^{2+}	[32]
Fabaceae/*Leucaena leucocephala* (Lam.) de Wit	Ethanolic extracts of leaves and acarbose (100, 200, 300, 400, and 500 μg/ml)	α-amylase assay	–	↓ α-amylase	Inhibiting absorption of glucose at the intestine	[33]
	Water extracts of fruits (0.1, 1.0, 10, and 100 μg/ml) and insulin (100 μM)	Preadipocytes of male Sprague-Dawley rats	–	↑adipogenesis, glucose uptake, GLUT-4, HSL ↓ Akt, PI3K, SREBP-1	Stimulating adipogenesis and enhancing glucose uptake	[34]
Solanaceae/*Physalis angulata* L.	Ethanolic extracts of leaves and stem (50, 100, and 200 μg/ml) and acarbose (100 μg/ml)	α-amylase assay	–	↓ α-amylase	Inhibiting absorption of glucose at the intestine and enhancing glucose uptake	[35]
	Ethanolic extracts of leaves and stems (50, 100, and 200 μg/ml), vehicle, and metformin (20 μg/ml)	LO-2 cells	–	↑ glucose uptake		
	Physalindicanol B and physalin D from *P. angulata* (10 μM), DMSO, and aicar (1 μM)	Glucose-induced HepG2 cells	–	↑ AMPK, ACC	Regulating FAS and glucose metabolism through AMPK pathway	[36]
	Physalindicanol B and physalin D from *P. angulata* (1, 3, and 10 μM) and DMSO			↓ FAS, SREBP-1c		
	Methanolic extracts of whole plants (500 mg/kg BW), distilled water (0.2 ml), and metformin (150 μg/kg BW) (p.o) for 14 days	–	Alloxan (100 mg/kg BW, i.p); male Wistar rats/ n = 5	↑ SOD ↓ glucose, fructosamine, HbA1c, MDA, creatinine, BUN	Antioxidant	[37]
		DPP-IV assay	–	↓ DPP-IV	Inhibiting DPP-IV activity	[16]

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	Ethanolic extracts of leaves and sitagliptin (0.2, 0.4, 0.8, 1.6, and 3.2 μg/ml)					
Rubiaceae/*Morinda citrifolia* L.	Water extracts of fruits (250 and 500 mg/ kgBW) and water	–	HFD and fructose; male Swiss mice/ n = 10 or 11	↑ insulin, HOMA-IR, HOMA-β, PPAR-α ↓ glucose, PPAR-γ, SREBP-1c, fetuin-A	Regulating genes of de novo lipogenesis	[38]
	Ethanolic extracts of fruits and acarbose (0.125–1.0 μg/ml)	α-amylase and α-glucosidase assays	–	↓ α-amylase, α-glucosidase	Inhibiting absorption of glucose at the intestine	[39]
	Ethanolic extracts of fruits (1 mg/ml), scopoletin (0.2 μM), and acarbose (1 mg/ml)	α-amylase and α-glucosidase assays	–	↓ α-amylase, α-glucosidase	Inhibiting absorption of glucose at the intestine and enhancing glucose uptake	[40]
	Ethanolic extracts of fruits (1 mg/ml), scopoletin (0.2 μM), metformin (100 μg/ml), and insulin (1 IU/ml)	HepG2 cells	–	↑ glucose uptake		
	Fermented of fruits juices sand vehicle, (p.o) twice a day for 12 weeks	–	HFD; male C57BL/6 mice/ n = 6	↓ glucose, HOMA-IR, AST, ALT, LDH, phosphofructokinase, PEPCK, G-6-P, Ga3P, FoxO1	Regulating glucose metabolism	[41]
	Ethanolic extracts of fruits (300 mg/kg BW), vehicle, and glyclazide (5 mg/kg BW), (p.o) for 30 days	–	STZ (50 mg/kg, i.p); Wistar rats/ n = 6	↑ insulin, hemoglobin, TP, GSH, SOD, CAT, GPx, GST ↓ glucose, Hb, blood urea, creatinine, AST, ALT, ALP, TBARS, hydroperoxides	Antioxidant	[42]
	Methanolic extracts of fruits (0.1, 0.5, 1.0, and 2.0 mg/ml), glybenclamide, and tolbutamide	BRIN-BD11 cells	–	↑ insulin release	Regulating insulinotropic activity	[43]
Myrtaceae/*Syzygium polyanthum* (Wight) Walp.	Ethanolic extracts of leaves (0.5, 2.0, and 5.0 mg/kg BW), vehicle, and glibenclamide (0.9 mg/kg BW) (p.o) for 8 weeks	–	Alloxan (125 mg/kg BW and HFD; Wistar rats/ n = 6	↓ glucose, AGEs	Regulating AGEs pathway	[44]
	Ethanolic extracts of leaves, acarbose, and diprotin (10, 25, 50, 100, and 150 μg/ml)	α-amylase, α-glucosidase, and DPP-IV assays	–	↓ α-amylase, α-glucosidase, DPP-IV	Inhibiting absorption of glucose at the intestine and DPP-IV activity	[45]
	Methanolic extracts of leaves (125, 250, 500, and 1000 mg/kg BW), normal saline 0.9% (10 ml/kg BW), and metformin (500 mg/kg BW) (p.o), twice daily for 6 days	–	STZ (55 mg/kg BW, i.p); male Sprague-Dawley rats/ n = 6	↑ glucose uptake ↓ glucose	Inhibiting absorption of glucose at the intestine and enhancing glucose uptake	[46]
	Methanolic extracts of leaves and acarbose (1 mg/ml)	Jejenum of male Sprague-Dawley rats/ n = 4	–	↓ glucose absorption		
Apocynaceae/*Catharanthus roseus* (L.) G.Don	Vindoline from *C. roseus* and acarbose (0.375 mM)	α-amylase and α-glucosidase assays	–	↓ α-amylase, α-glucosidase	Inhibiting absorption of glucose at the intestine and antioxidant	[47]
	Vindoline from *C. roseus* (0.125 mM) and vehicle	RIN-5F cells	–	↑ insulin release		
	Vindoline from *C. roseus*, vehicle, and H_2O_2	RIN-5F cells	–	↓ ROS, TNF-α		
	Ethanolic extracts of leaves (50 mg/kg BW), normal saline (0.9%), and glimepiride (0.1 mg/kg BW), (p.o) for 28 days	–	STZ (50 mg/kg BW, i.p); male Wistar rats/ n = 6	↑ insulin, glycogen, GST, CAT, SOD, GPx ↓ glucose, LPO	Regulating insulin secretion and glycogen storage, and antioxidant	[48]
	Vindoline (20 mg/kg BW), vehicle, and glibenclamide (5 mg/kg BW), p.o for 8 weeks	–	10% fructose and STZ (40 mg/kg BW, i.p); male Wistar rats/ n = 8	↑ insulin, ORAC, SOD, CAT, GSH, Bcl-2 ↓ glucose, TG, LPO, TNF-α, IL-6, caspase-9	Anti-oxidant and anti-inflammation	[49]
	Aqueous alkaloid-free extracts of stems (10 and 100 μg/ml),	RINm5F cells	–	↑ insulin expression	Stimulating insulin secretion	[50]

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Table 1 (*Continued*)

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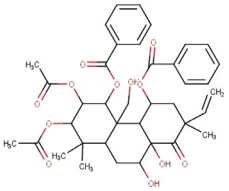
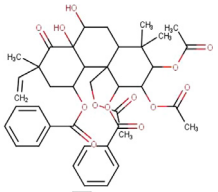
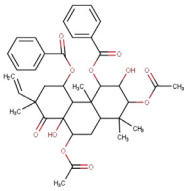
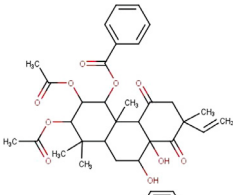
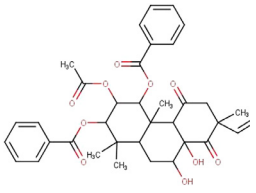
	vehicle, and glibenclamide (4 μM)					
	Ethanolic extracts of leaves (100 and 200 mg/kg BW), and metformin (100 mg/kg BW), p.o for 4 weeks	–	STZ (90 mg/kg BW, i.p); male Wistar rats/ n = 6	↑ GLUT-2, GLUT-4 ↓ glucose, TC, creatinine, ALP, AST, ALT, BUN	Regulating glucose transport	[51]
	Vindogentianine and insulin	β-TC6 and C2C12 cells	–	↑ glucose uptake	Enhancing glucose uptake and inhibiting PTP1B activity	[52]
	Vindogentianine, 3-hexadecanoyl-5-hydroxymethyl tetronic acid, and ursolic acid	PTP1B enzyme		↓ PTP1B		
	Suspended of leaves powder (100 mg/kg BW) and vehicle	–	Fructose-induced; male Wistar rats/ n = 8	↑ hexokinase, glycogen phosphorylase, lipoprotein lipase ↓ glucose, TG, HOMA, pyruvate kinase, G-6-P, fructose-1,6-bisphosphatase, TC, TG, FFA, phospholipids, malic enzyme, FAS	Regulating carbohydrate and lipid metabolisms	[53]
	Ethanolic extract (30 and 100 mg/ml, and DMSO	Cos7 cells	–	↑ PPAR-α, PPAR-γ	Regulating PPAR	[54]
Myrtaceae/*Syzygium cumini* (L.) Skeels	Fractions of ethanolic extracts of leaves and acarbose	α-amylase and α-glucosidase assays	–	↓ α-amylase, α-glucosidase	Inhibiting absorption of glucose at the intestine, antiglycation, anti-inflammatory, and antioxidant	[55]
	Fractions of ethanolic extracts of leaves and orlistat	Lipase assay	–	↓ lipase		
	Fractions of ethanolic extracts of leaves and quercetin	Glycation, ROS, lipid peroxidation assays	–	↓ glycation, ROS, lipid peroxidation		
	Methanol fractions of seeds	DPP-IV assay	–	↓ DPP-IV	Inhibiting DPP-IV activity	[56]
	Water extracts of seeds (100, 200, and 400 mg/kg BW), normal saline 0.9% (3.0 ml/kg BW), and metformin (100 mg/kg BW), p.o for 21 days	–	STZ (40 mg/kg BW, i.p) and HFD; male Wistar rats/ n = 10	↑ β-cell function, SOD, CAT, GSH, PPAR-α, PPAR-γ ↓ glucose, HOMA-IR, HOMA-B, TNF-α, TG, TC, LDL, TBARS	Protecting β-cell, antioxidant, and enhancing glucose uptake through PPAR pathway	[57]
	Methanolic extracts of seeds and vitalboside A (1 ng/ml to 10 μg/ml)	PTP1B assay	–	↓ PTP1B	Inhibiting PTP1B activity and enhancing glucose uptake through PI3K/ Akt pathway	[58]
	Methanolic extracts of seeds (1 ng/ml to 10 μg/ml), rosiglitazone (50 μM), and insulin (100 nM)	3T3-L1 cells and L6 cells	–	↑ IR-β, IRS-1, PI3K, Akt, GLUT-4, GSK-β		
	Ethyl acetate fractions of methanolic extracts of seeds and glibenclamide (20 mg/kg BW)	Sucrase and maltase assays	–	↓ sucrase, maltase	Inhibiting maltase and sucrase at the intestine	[59]
	Water extracts of leaves (100, 200, and 500 μg/ml), rutin (40, 80, and 120 μM), gallic acid (50, 100, and 200 μM), and chlorogenic acid (20, 80, and 120 μM)	Glucose-induced erythrocytes	–	↓ adenosine deaminase	Inhibiting adenosine deaminase	[60]
	Ethanolic extracts of seeds (500 and 1000 mg/kg BW) and vehicle	–	STZ (40 and 70 mg/kg BW); male Wistar rats/ n = 5	↑ insulin, insulin release, glycogen, HDL, hexokinase ↓ G-6-P, TC, LDL, VLDL, TG	Promoting glycogen synthesis, enhancing glucose uptake through PPAR pathway, and regulating glucose metabolisms	[61]
	Ethanolic extracts of seeds (3, 10, and 30 mg/l), vehicle, and rosiglitazone (20 μM)	3T3-L1 cells	–	↑ PPAR-α, PPAR-γ		
Arecaceae/*Areca catechu* L.	Fractions of acetone extracts of nuts (0.1, 1.0, 10 μg/ml), vehicle, and insulin (10 nM)	Dexamethasone-induced primary hepatocytes from male C57BL/6 mice	–	↓ PEPCK, G-6-Pase	Regulating gluconeogenesis	[62]

Abbreviations: 3HKYN, 3-hydroxykynurenine; 4-HNE, 4-hydroxynonenal; ACC, acetyl-CoA carboxylase; ADP, adenosine diphosphate; AGEs, advanced glycation end-products; ALP, alkaline phosphatase; ALT, alanine transaminase; AMPK, AMP-activated protein kinase; ANP, atrial natriuretic peptide; AP-1, activator protein-1; AST, aspartate aminotransferase; ATP, adenosine triphosphate; Bax, Bcl-2-associated X; Bcl-2, B-cell lymphoma-2; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CAT, catalase; DMSO, dimethyl sulfoxide; DPP-IV, dipeptidyl peptidase-IV; Egr-1, early growth response-1; FAS, fatty acid synthase; FBG, fasting blood glucose; FFA, free fatty acid; FoxO1,

Forkhead box-O1; G-6-P, glucose-6-phosphate; G-6-PD, glucose-6-phosphate dehydrogenase; Ga3P, glyceraldehyde 3-phosphate; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; GATA3, GATA binding protein 3; GLP-1, glucagon like peptide-*1*; GLUT, glucose transport; GPx, glutathione peroxidase; GSH, glutathione; GSK, glycogen synthase kinase; GST, glutathione transferase; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; HFD, high fat diet; HO-1, heme oxygenase-1; HOMA, homeostatic model assessment; HSL, hormone sensitive lipase; ICAM, intercellular adhesion molecule; IFN, interferon; IL, interleukin; iNOS, inducible nitric oxide synthase; IR, insulin receptor; IRS, insulin receptor substrate; KYN, kynurenine; KYNA, kynurenine acid; LBP, LPS-binding protein; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; LPO, lipid peroxidation; LPS, lipopolysaccharides; MCP-1, monocyte chemoattractant protein-1; MDA, malondialdehyde; NF-κB, nuclear factor-κB; Nox, NADPH oxidase; NRF, nuclear factor erythroid 2-related factor; ORAC, oxygen radical absorbance capacity; p.o, per oral; PAI-1, plasminogen activator inhibitor type 1; PDX-1, pancreatic and duodenal homeobox 1; PI3K, phosphoinositide-3-kinase; PKC, protein kinase C; PLC, phospholipase C; PPAR, peroxisome proliferator-activated receptor; PTP1B, Protein tyrosine phosphatase 1B; ROR-γt, retinoic acid-related orphan receptor-γt; ROS, reactive oxygen species; SOCS3, suppressor of cytokine signaling 3; SOD, superoxide dismutase; SREBP-1, sterol regulatory-element binding protein-1; STZ, streptozotocin; TBARS, thiobarbituric acid reactive substances; TC, total cholesterol; TG, triglyceride; TGF, transforming growth factor; Th1/Th2/Th17, T helper cell type 1/ T helper cell type 2/ T helper cell type 17; TLR, toll-like receptors; TNF, tumor necrosis factor; TP, total protein; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor; VLDL, very-low-density lipoprotein; ZO-1, zona occludin-1.

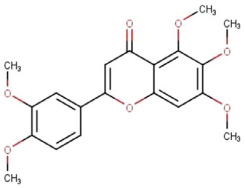
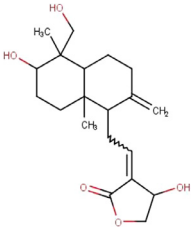
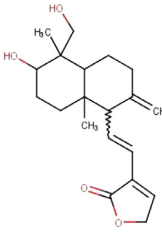
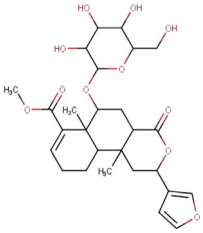
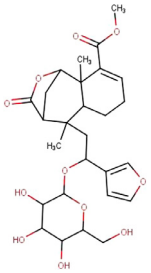
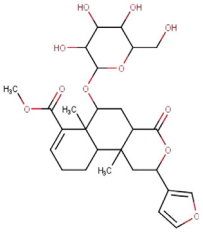
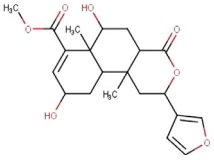
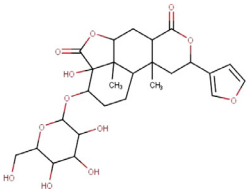
Notes. [1] (Lokman et al., 2019); [2] (Nguyen et al., 2019); [3] (Rao et al., 2014); [4] (Mohamed et al., 2013); [5] (Mohamed et al., 2012); [6] (Gherardelli et al., 2021); [7] (Jaiyesimi et al., 2020); [8] (M. M. Kumar et al., 2020); [9] (S. S. Zhang et al., 2020); [10] (Thengyai et al., 2020); [11] (M. P. M.P. Kumar et al., 2020); [12] (Chen et al., 2020); [13] (Su et al., 2020); [14] (Liang et al., 2018); [15] (Thakur et al., 2016); [16] (Riyanti et al., 2016); [17] (Yu et al., 2015); [18] (Lan et al., 2013); [19] (Zhang et al., 2013); [20] (Saifudin et al., 2013); [21] (Jin et al., 2011); [22] (Lee et al., 2010); [23] (Subramanian et al., 2008); [24] (Dandu and Inamdar, 2008); [25] (Hsu et al., 2004); [26] (Adnan et al., 2018); [27] (Abu et al., 2018); [28] (Xu et al., 2017); [29] (Hamid et al., 2015); [30] (Lokman et al., 2013); [31] (Ruan et al., 2013); [32] (Noor and Ashcroft, 1998); [33] (Renganathan et al., 2021); [34] (Kuppusamy et al., 2014); [35] (Nguyen and Vo, 2020); [36] (Hoa et al., 2020); [37] (Adewoye et al., 2016); [38] (Inada et al., 2020); [39] (Rao, 2018); [40] (Khamis et al., 2015); [41] (Nerurkar et al., 2012); [42] (Rao and Subramanian, 2009); [43] (Hamid et al., 2008); [44] (Wahjuni et al., 2018); [45] (Elya et al., 2015); [46] (Widyawati et al., 2015); [47] (Goboza et al., 2020); [48] (Alkreathy and Ahmad, 2020); [49] (Goboza et al., 2019); [50] (Espejel-Nava et al., 2018); [51] (Al-Shaqha et al., 2015); [52] (Tiong et al., 2015); [53] (Rasineni et al., 2013); [54] (Rau et al., 2006); [55] (Franco et al., 2020); [56] (Syama et al., 2018); [57] (Sharma et al., 2017); [58] (Thiyagarajan et al., 2016); [59] (Jana et al., 2015); [60] (De Bona et al., 2014); [61] (Sharma et al., 2008); [62] (Huang et al., 2013).

Table 2
Phytochemicals with *in vitro*/ *in vivo* antidiabetic activities.

Family/ Species	Sources	Class of compounds	Phytochemicals	Chemical structures	References
Lamiaceae/*Orthosiphon aristatus* (Blume) Miq.	Aerial parts	Pimarane diterpenes	Siphonol B		[1]
			Siphonol D		
			Orthosiphol B		
			Orthosiphol F	N/A	
			Orthosiphol G	N/A	
			Orthosiphol I		
			Orthosiphol N		

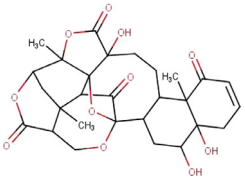
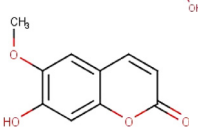
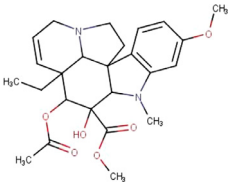
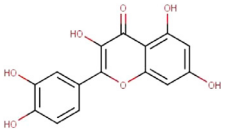
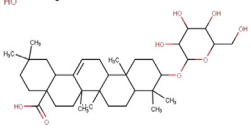
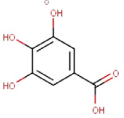
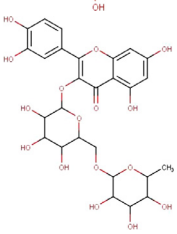
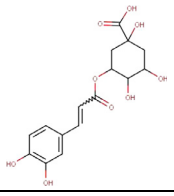
(*continued*)

Table 2 (*Continued*)

Family/ Species	Sources	Class of compounds	Phytochemicals	Chemical structures	References
	Leaves	Flavonoids	Sinensetin		[2]
Acanthaceae/*Andrographis paniculata* (Burm.f.) Nees	Commercial	Diterpenoid lactones	Andrographolide		[3]
	Plant materials	Diterpenes	14-Deoxy-11,12-didehydroandrographolide		[4]
Menispermaceae/*Tinospora crispa* (L.) Hook.f. & Thomson	Stems	Diterpenoid glycosides	Tinocrisposide		[5]
	Commercial	Diterpenoids	Borapetoside E		[6]
	Vines	Diterpenoids	Borapetoside C		[7]
	Stems	Diterpenoids	Borapetol B		[8]
	Vines	Diterpenoids	Borapetoside A		[9]

(*continued*)

Table 2 (*Continued*)

Family/ Species	Sources	Class of compounds	Phytochemicals	Chemical structures	References
Solanaceae/*Physalis angulata* L.	Plant materials	Steroids	Physalindicanol B	N/A	[10]
	Plant materials	Steroids	Physalin D		[10]
Rubiaceae/*Morinda citrifolia* L.	Fruits	Coumarins	Scopoletin		[11]
Apocynaceae/*Catharanthus roseus* (L.) G.Don	N/A	Indole alkaloids	Vindoline		[12]
	Leaves	Indole alkaloids	Vindogentianine	N/A	[13]
Myrtaceae/*Syzygium cumini* (L.) Skeels	Leaves	Flavonoids	Quercetin		[14]
	Seeds	Triterpenoid saponins	Vitalboside A		[15]
	Leaves	Phenolics	Gallic acid		[16]
	Leaves	Flavonoids	Rutin		[16]
	Leaves	Phenolics	Chlorogenic acid		[16]

Notes. [1] (Nguyen et al., 2019); [2] (Mohamed et al., 2012); [3] (Gherardelli et al., 2021); [4] (Chen et al., 2020); [5] (Adnan et al., 2018); [6] (Xu et al., 2017); [7] (Hamid et al., 2015); [8] (Lokman et al., 2013); [9] (Ruan et al., 2013); [10] (Hoa et al., 2020); [11] (Khamis et al., 2015); [12] (Goboza et al., 2020); [13] (Tiong et al., 2015); [14] (Franco et al., 2020); [15] (Thiyagarajan et al., 2016); [16] (De Bona et al., 2014).

patients, even causing death, threatening public health in the world (Saeedi et al., 2019; Shabab et al., 2021; Tripathy et al., 2021). Several antidiabetic agents help to control DM, but no cure is yet available for complete recovery from the disease (Tripathy et al., 2021). Furthermore, the treatment of DM has been enhancing day-by-day due to new research and development that enhance the health and quality of life of diabetic patients (Tripathy et al., 2021). Conventional diabetic drugs are undoubtedly effective but correlated with certain complications or side effects, thus promoting studies to develop safer, more efficient, and more affordable diabetic treatments (Tripathy et al., 2021).

Medicinal plants can potentially treat DM due to the effectiveness stage of diabetes progression and its complications, toxicity and safety profile, and availability (Tripathy et al., 2021). Indonesia is known for its biodiversity and ethnic richness. Numerous reports discussed traditional medicine systems, including the ethnopharmacological studies of antidiabetic properties. In this study, we reported the past and present findings and the future perspective of Indonesian antidiabetic plants and highlighted the ethnopharmacological data, preclinical trials (*in vitro* or *in vivo*), phytochemical issues, clinical trials, and toxicological assessments. Further, this work discussed that medicinal plants used to treat DM might be used for further

research to explore the discovery and development of phytomedicines.

Reports about the traditional medicine used to treat DM are available from most provinces in Indonesia. Meanwhile, provinces with rich culture and a lack of antidiabetic ethnopharmacological studies, such as the Special Region of Yogyakarta and Bali (Heinrich et al., 2012), can be explored in more detail, promising research. Moreover, the database for Indonesian medicinal plants is unavailable despite the rapid growth in using various herbal products. That database can provide comprehensive public information and prevent knowledge later generations. Other countries developed several herbal medicine databases, such as Medplant online (http://www.medplant.mahidol.ac.th) and Thaicrudedrug (http://www.thaicrudedrug.com) in Thailand, and VOLKSMED database (http://www.volksmed.org/) in Austria (Vogl et al., 2013; Khoomrung et al., 2017).

The present study also highlighted important information that was unexplored in previous ethnopharmacological surveys. This information supports for further investigations by scholars and practitioners in the pharmaceutical industry to develop phytomedicines and provide comprehensive public information to communities. Thus, such information should be included in further ethnopharmacological studies to strengthen their research quality. Several improvements that can be applied in ethnopharmacological surveys, such as those in herbal recipes and proper dosage in communities, should be checked to prove the pharmacological activities of medicinal plants; improper dosage during applications can lead to severe complications (Sadia et al., 2018). Moreover, information on mono-herbal or poly-herbal recipes is vital given that poly-herbal recipes are frequently used to treat DM and remains a tradition to date (Liyanagamage et al., 2021). Poly-herbals are used to attain synergistic effects to enhance their effectivity (Sadia et al., 2018). On the other hand, information about dosage applied in communities, provided through calculation of equal amounts of plant materials according to ethnopharmacological surveys, is required to decide the dosage in preclinical trials (Liyanagamage et al., 2021). Other information about dosage administered in a day, frequency and duration of treatment, and route of application can also be explored, especially in pharmacological experiments (Mechchate et al., 2020).

Ethnopharmacological studies about medicinal plants to treat DM in Indonesia revealed the five most-cited families. These families were Asteraceae, Fabaceae, Lamiaceae, Poaceae, and Malvaceae. Previous ethnopharmacological surveys related to DM in other countries also mentioned these families as the most commonly used plant family. The Asteraceae family contributes to drug discovery related to diabetes and is the most commonly used plant to treat DM in South Africa (Cock et al., 2021). An ethnopharmacological study of DM treatment in Attock district, Pakistan, revealed Fabaceae as the most commonly used plant family (Ahmad et al., 2009). Previous ethnopharmacological surveys related to DM in Urmia (Northwest Iran) and the city of Chtouka Ait Baha and Tiznit (Morocco) presented Lamiaceae as the most represented family (Bahmani et al., 2014; Barkaoui et al., 2017). Poaceae was the most commonly used plant family for DM treatment in Thailand (Phumthum and Balslev, 2018). Recently, no previous ethnopharmacological report mentioned Malvaceae as the most represented family in DM management. Meanwhile, Malvaceae was one of the third highest plant families used for DM management in Vhembe district, South Africa (Mudau et al., 2022).

Prior ethnopharmacological surveys provided vague identifications of botanical plants. This step is crucial in ethnopharmacological surveys, in addition to the preparation and deposition of voucher specimens (Weckerle et al., 2018). Leaves are the most used plant parts in previous ethnopharmacological surveys. One survey exhibited the preference for leaves by herbalists and traditional healers due to the sustainability of their supply as medicinal plant materials (Moshi et al., 2012). In addition, plant material conditions (fresh or dried plant material), plant maturity, season and collection period, ecological and physiological plant aspects, post harvesting technique, processing, storage, mode and duration of preparation, and others, also influence phytochemical compounds (Drinkwater et al., 2015; Donno et al., 2016; Figueroa-Pérez et al., 2018; Sadia et al., 2018).

Pharmacological validation of antidiabetic plants should be further explored at the molecular level of their mechanisms of action and diabetic complications. The steps prior to conducting pharmacological experiments comprise preparing extract, fraction, or isolated compound for extraction treatment of influential phytochemical and pharmacological activities (Ng et al., 2020). On the other hand, the selection of preclinical models is essential, given that each model has advantages and disadvantages (Shabir et al., 2020). Plants with abundance exploration in preclinical and clinical trials can be developed with straightforward, transparent, and proper standardization methods at the pharmacy industrial levels. Most plants in this study were not explored for their active phytochemical compounds. Thereby, information on active compounds is useful in deciding the proper standardization methods and possibility of interaction with other herbals, nutritionals, and drugs.

Medicinal plants are complex matrices consisting of various chemical compounds of plants (Zhu et al., 2018). These phytochemicals influence the prevention and/ or cure of several human diseases due to their pharmacological activities (Rohman et al., 2020; Rahman et al., 2021). Of 14 selected medicinal plants, only ten plants have elucidated a single compound in diabetic activities (Table 2). The data from the preclinical screening of selected Indonesian antidiabetic plants (Table 1) showed that a plant could have more than one phytochemical compound responsible for antidiabetic activities. Active compounds that contribute to the therapeutic activities can be applied as the lead compound to develop further natural drugs to improve the pharmacological activities and maintain the consistency of natural drugs through the quality control process (Yang et al., 2017; Xu et al., 2019).

Pharmacological activities can be optimized by the optimal extraction process, such as solvent types, extraction methods, extraction times, and other parameters (Zohra et al., 2019; Ji et al., 2020). Among the selected medicinal plants, the most are dominated by terpene compounds (Table 2). Primary backbones of terpenes structures (linear and cyclized terpenes without decoration) mostly consisted of hydrocarbons, so these compounds are non-polar (Jiang et al., 2016). Meanwhile, many terpenoids are decorated with one or multiple polar groups, significantly increasing polarity (Jiang et al., 2016). The extraction process of terpenes depends on their polarities (Louie et al., 2020). Non-polar terpenes are best extracted with a non-polar solvent (for instance: hexane); meanwhile, more polar terpenes are suggested to be extracted with a more polar solvent (for instance: methanol) (Jiang et al., 2016; Louie et al., 2020). Andrographolide isolated from *A. paniculata* is one of the compounds belonging to terpenes compounds, specifically diterpenoid lactones (Gherardelli et al., 2021). Previous studies revealed that *A. paniculata* extraction could be extracted using methanol (soxhlation), methanol (maceration), and ethanol (Rafi et al., 2014; Bhan et al., 2017; Syukri et al., 2018). On the other hand, other classes of secondary metabolites, including flavonoids, steroids, coumarins, alkaloids, phenolics, and others, also have specific polarity values. Therefore, a suitable solvent is needed to obtain the intended active phytochemical compounds.

On the other hand, toxicological issues of herbal medicines must be addressed to avoid their toxicities, harmful properties, and adverse effects and to aid herbal medicine providers in handling toxicity and deciding on appropriate safety precautions. Two plants of 10 selected plants had no assessment on toxicity studies, *i.e., T. crispa* and *P. angulata* (Table 4). Even though *T. crispa* revealed no toxicity studies data, a case report in Thailand showed adverse effects.

Table 3
Clinical trials of selected Indonesian antidiabetic plants.

Family/Species	Extract/fraction(s) or compounds, dose, and duration	Participants (n)	Results	Outcomes	References
Acanthaceae/*Andrographis paniculata* (Burm.f.) Nees	Capsules (300 mg) of powders of leaves, 1–2 capsules, once a day for 1 week	T2DM patients (ages 28–65), *n* = 20	↓ glucose, uric acid, TC	Improving metabolic profile	[1]
	Tablets combination of water extracts of leaves of *A. paniculata* and *S. polyanthum* (900 mg/ day) and metformin (1000 mg/ day), for 8 weeks	T2DM patients (ages ≥30), *n* = 54	↓ BMI, FPG, PPG, TC, LDL	Improving glucose and lipid profile	[2]
	Combination of whole plants of *A. paniculata*, whole plants of *Phyllanthus niruri*, whole plants of *Eclipta alba*, and roots of *Picrorhiza kurroa* (250 mg of each component), for 16 weeks	NIDDM patients (ages 30–65), *n* = 15	↓ FPG, PPG	Improving glucose profile	[3]
	Combination of ethanolic extracts of *Pterocarpus indicus* leaves (20%), *Momordica charantia* fruits (10%), *Phaseolus vulgaris* fruits (40%), and *A. paniculata* (30%) (22 mg/kg BW) and glibenclamide (5 mg), once daily for 4 weeks	T2DM patients (ages 30–65), *n* = 41	↓ FPG, PPG	Improving glucose profile	[4]
	Capsules (600 mg) of powders of aerial parts, 2 capsules in a day, for 12 weeks	T2DM patients (ages 35–70), *n* = 20	↓ HbA1c, fasting insulin	Improving metabolic profile	[5]
Menispermaceae/*Tinospora crispa* (L.) Hook.f. & Thomson	Capsules (125 and 250 mg) of ethanolic extracts of stems and without treatment, twice in a day for 2 weeks	Healthy subjects (*n* = 10) and type 2 DM patients (*n* = 10), (ages 32–64)	↓ glucose, insulin	No differences changes	[6]
	Capsules (1000 mg) of powders of stems and placebo, 3 capsules in a day for 6 months	T2DM patients (ages ≥35), *n* = 40	↑glycosylated hemoglobin ↓ FPG	Improving glucose profile	[7]
Rubiaceae/*Morinda citrifolia* L.	Fruits juices (2 ml/kg BW in a day), for 8 weeks	T2DM patients, *n* = 20	↑ C-peptide ↓ glucose, HbA1c	Improving glucose and metabolic profiles	[8]
Myrtaceae/*Syzygium polyanthum* (Wight) Walp.	Capsules (300 mg) of powders of leaves, 1–2 capsules, once a day for 1 week	T2DM patients (ages 28–65), *n* = 20	↓ glucose, uric acid, TC	Improving metabolic profile	[1]
Myrtaceae/*Syzygium cumini* (L.) Skeels	Powders (600 mg) of *Gymnema sylvestre, Tinospora cordifolia,* and *S. cumini* and metformin (500 mg), twice daily for 12 weeks	T2DM patients (ages 18–65), *n* = 60	↓ FPG, PPG, HbA1c	Improving glucose profile	[9]
	Powders (5000 mg) of seeds and placebo, twice daily for 90 days	T2DM patients, *n* = 99	↓ FPG, PPG, HbA1c	Improving glucose profile	[10]
	Powders of seeds (10 g/day) and placebo, for 6 months	T2DM patients, *n* = 25	↑ GSH, SOD ↓ FPG, PPG, HbA1c	Improving glucose profile and antioxidant	[11]
	Extracts of leaves (100 and/ or 200 μg/ml) and placebo, *in vitro*	Healthy subjects (*n* = 20) and type 2 DM patients (*n* = 30)	↑ NP-SH ↓ ADA, AChE, TBARS	Reducing inflammation and oxidative stress	[12]
	Ethanolic extracts of leaves (100 and/ or 200 μg/ml) and placebo, *in vitro*	Healthy subjects (*n* = 17) and type 2 DM patients (*n* = 30)	↓ ADA, 5′NT, TBARS	Reducing inflammation and oxidative stress	[13]
	Glucaffect^{TM} (12 g) which contain 500 mg of extracts of *S. cumini* and placebo, 4 dosages/ day for 8 weeks	T2DM patients (ages 30–60), *n* = 50	↓ FPG, HbA1c, BMI	Improving glucose profile	[14]
	Water extracts of leaves (3–1000 μg/ml) and placebo, *in vitro*	T2DM patients, *n* = 26	↓ ADA	Modulating enzymes related to bioactivity of insulin	[15]
	Tea leaves (20 g/day in 1000 ml), glyburide, and placebo, for 28 days	T2DM patients, *n* = 27	↓ FBG	Improving glucose profile	[16]
		T2DM patients (ages 40–60), *n* = 10	↑ HDL ↓ glucose, LDL, TC, TG	Improving glucose and lipid profile	[17]

(*continued*)

Table 3 (*Continued*)

Family/Species	Extract/fraction(s) or compounds, dose, and duration	Participants (n)	Results	Outcomes	References
	Water extracts of leaves (30 ml) and control, three times in a day for 8 days Decoction of tea leaves (2 g in 250 ml) and placebo tea, for 2 weeks	Healthy subjects (n = 30)	↔ glucose	No differences changes	[18]

Abbreviations: 5′NT, 5′-nucleotidase; AChE, acetylcholinesterase; ADA, adenosine deaminase; BMI, body mass index; DM, diabetes mellitus; FPG, fasting plasma glucose; GSH, glutathione; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NIDDM, non-insulin-dependent diabetes mellitus; NP-SH, non protein thiol groups; PPG, postprandial glucose; SOD, superoxide dismutase; T2DM, type 2 diabetes mellitus; TBARS, thiobarbituric acid reactive substances; TC, total cholesterol; TG, triglyceride.
Notes. [1] (Ischak and Botutihe, 2020); [2] (Widjajakusuma et al., 2019); [3] (Kajaria et al., 2017); [4] (Azam et al., 2016); [5] (Agarwal et al., 2005); [6] (Klangjareonchai and Roongpisuthipong, 2012); [7] (Sangsuwan et al., 2004); [8] (Algenstaedt et al., 2018); [9] (Ahmad et al., 2021); [10] (Sidana et al., 2017); [11] (Shivaprakash et al., 2011); [12] (De Bona et al., 2011); [13] (De Bona et al., 2010); [14] (Belcaro et al., 2009); [15] (Bopp et al., 2009); [16] (Teixeira et al., 2006); [17] (Safdar et al., 2006); [18] (Teixeira et al., 2000).

Table 4
Toxicological assessments of selected Indonesian antidiabetic plants.

Family/ Species	Extract/fraction(s) or compounds, dose/ concentration with the route of administration and duration	Model/sample size	Effects	References
Lamiaceae/*Orthosiphon aristatus* (Blume) Miq.	Nanoliposomes of ethanolic extracts of leaves (500 μg/ml)	Ames test, *Salmonella typhimurium*	Non mutagenic	[1]
	Nanoliposomes of ethanolic extracts of leaves (5000 mg/kg BW) and control	Acute toxicity model, female Sprague-Dawley rats/ n = 5	No mortality and no observed signs of toxicity	
	Nanoliposomes of ethanolic extracts of leaves (250, 500, and 1000 mg/kg BW) and water	Subchronic toxicity model, male and female Sprague-Dawley rats/ n = 10	No mortality and no observed signs of toxicity	
	Water extracts of leaves (250, 500, 1000, and 2000 mg/kg BW) and control	Reproductive toxicology model, female Sprague-Dawley rats/ n = 21	No toxic to embryos	[2]
Acanthaceae/*Andrographis paniculata* (Burm.f.) Nees	Ethanolic extracts of leaves (300, 2000, and 5000 mg/kg BW) and control	Acute toxicity model, male and female Swiss mice/ n = 10	No mortality and no observed signs of toxicity	[3]
	Methanolic extracts of leaves (16 to 5000 μg/ml)	Ames test, *S. Typhimurium*	Non mutagenic	[4]
	Methanolic extracts of leaves (8.8 to 345 μg/ml)	Chromosome aberration test, CHO-K1 cells	Non genotoxic	
	Methanolic extracts of leaves (8.8 to 345 μg/ml)	Micronucleus test, CHO-K1 cells	Non genotoxic	
	Methanolic extracts of leaves (5000 mg/kg BW) and CMC 1%	Acute toxicity model, female Wistar rats/ n = 10	No mortality and no observed signs of toxicity	
	Ethanolic extracts of herbs (20, 200 and 1000 mg/kg BW) and saline, p.o	Subchronic testicular toxicity model, male Sprague-Dawley rats/ n = 6	No toxicity of testicular organs	[5]
Fabaceae/*Leucaena leucocephala* (Lam.) de Wit	Water extracts of leaves (400 and 600 mg/kg BW) and distilled water, p.o	40 days treatment, male Sprague-Dawley rats/ n = 5	Toxic potency in male organs especially testicular tissues	[6]
Rubiaceae/*Morinda citrifolia* L.	Fermented water fruit juices (1.2 and 9.0 ml/kg BW) and distilled water, p.o	Subchronic toxicity model, male and female Sprague-Dawley rats	No mortality and no observed signs of toxicity	[7]
	Water extracts of leaves and fruits (1 and 2 mg/ml), p.o	Chronic toxicity model, female ICR mice/ n = 5	No mortality and no observed signs of toxicity	[8]
	Ethanolic extracts of fruits (100, 200, 500, 1000, and 2000 mg/kg BW), p.o	Acute toxicity model, male and female Wistar rats/ n = 3	No mortality and no observed signs of toxicity	[9]
	Ethanolic extracts of seeds and green tea	Brine Shrimp Lethality Assay, *Artemia salina*	Non toxic	[10]
	Ethanolic extracts of seeds (1000 mg/kg BW) and NaCl 0.9%	Subacute toxicity model, male and female Sprague-Dawley rats/ n = 10	No mortality and no observed signs of toxicity	
	Ethanolic extracts of seeds (1000 μg/ml), 4-nitroquinoline 1-oxide (5 μg/ml), and aminoanthracene (100 μg/ml)	Primary DNA damage test, *Escherichia coli*	Non genotoxic	
	Infusion of leaves (3700 μg/ml)	Mutation assay, *S. Typhimurium*	Non mutagenic	[11]
	Water extracts of fruits (7.5, 75, and 750 mg/kg BW) and vehicle 5 ml/kg BW, p.o	Reproductive toxicology model, female Wistar rats	Induction of reproductive toxicology	[12]

(*continued*)

Table 4 (*Continued*)

Family/ Species	Extract/fraction(s) or compounds, dose/ concentration with the route of administration and duration	Model/sample size	Effects	References
	Freeze-dried fruits (1.72, 3.43, 6.86 g/ kg BW) and vehicle, p.o	Prenatal toxicology model, male and female Sprague-Dawley rats	No toxicity to the developing embryo/ fetus	[13]
Myrtaceae/*Syzygium polyanthum* (Wight) Walp.	Methanolic extracts of leaves (400, 1000, and 2000 mg/kg BW) and distilled water, p.o	Subacute toxicity model, male and female Sprague-Dawley rats/n = 10	No mortality and slight toxicity at liver function	[14]
	Ethanolic extracts of leaves (100, 400, and 1000 mg/kg BW) and 2% of arabic gum, p.o	Subchronic toxicity model, male and female Wistar rats	No mortality and fatty liver and necrosis in female rats	[15]
	Ethanolic, methanolic, hexane extracts, positive, and negative controls	Comet assay, human peripheral blood mononuclear cells	No DNA damage	[16]
Apocynaceae/*Catharanthus roseus* (L.) G.Don	Water extracts and methanol-dichloromethane extracts of roots (0.031, 0.063, 0.125, 0.25, 0.5 and 1 mg/ml) and DMSO	Brine Shrimp Lethality Assay, *Artemia salina*	Non toxic	[17]
	Water extracts and methanol-dichloromethane extracts of roots (5 mg/ml) and DMSO	Ames test, *S. Typhimurium*	Non mutagenic	
	Ethanolic extracts of leaves (5, 50, 300, and 2000 mg/kg BW)	Acute toxicity model, female Wistar rats/ n = 5	No mortality and showed liver and renal toxicity	[18]
	Leaves and flowers	Acute toxicity model, sheep	Observed signs of toxicity	[19]
Myrtaceae/*Syzygium cumini* (L.) Skeels	1%, 5%, and 10% of tincture	Zebrafish model	Mortality of zebrafish embryos in 10% of tincture	[20]
	Water extracts of barks (300, 2000, and 5000 mg/kg BW) and distilled water	Acute toxicity model, male and female Swiss mice/ n = 6	No mortality and no observed signs of toxicity	[21]
Arecaceae/*Areca catechu* L.	Methanolic extracts of seeds (30–1000 mg/l)	Brine Shrimp Lethality Assay, *Artemia salina*	Toxic at 347.86 mg/l	[22]
	Water extracts of seeds (750, 1500, and 4500 mg/kg BW) and distilled water, p.o	Subchronic toxicity model, male and female Wistar rats/ n = 30	High dose at long-term of administration	[23]
	Water extracts of seeds (166.7, 500, and 1500 mg/kg BW) and steril water, p.o	13 weeks treatment, male and female F344/N rats/ n = 20	Incidence of abnormal clinical signs at above of 500 mg/kg BW	[24]
	Water extracts of seeds (15 g/kg BW) and water, p.o	Acute toxicity model, female Sprague-Dawley rats	No mortality and no observed signs of toxicity	[25]
	Arecoline (0.2, 2, 20, and 200 μg) and vehicle	Early pregnancy toxicity model, ICR mice/ n = 4 or 5	Toxic to mouse embryos	[26]

Abbreviations: DNA, deoxyribonucleic acid; NaCl, natrium chloride; p.o, per oral.
Notes. [1] (Shafaei et al., 2015); [2] (Muhammad et al., 2013); [3] (Worasuttayangkurn et al., 2019); [4] (Worasuttayangkurn et al., 2019); [5] (Burgos et al., 1997); [6] (Burawat et al., 2016); [7] (Chaiyasut et al., 2018); [8] (Shalan et al., 2017); [9] (Radhakrishnan et al., 2015); [10] (West et al., 2011); [11] (West et al., 2009); [12] (Müller et al., 2009); [13] (West et al., 2008); [14] (Harun et al., 2021); [15] (Sumiwi et al., 2019); [16] (Jumaat et al., 2017); [17] (Ramulondi et al., 2019); [18] (Vutukuri et al., 2017); [19] (Aydogan et al., 2015); [20] (Sharma et al., 2021); [21] (Yele and Veeranjaneyulu, 2010); [22] (Rasyid et al., 2020); [23] (Lin et al., 2018); [24] (Kim et al., 2018); [25] (Sari et al., 2014); [26] (Liu et al., 2011).

Tinocrispa crispa caused gastrointestinal disorders (abdominal pain, constipation, and abdominal discomfort), liver and biliary disorders (hepatitis), and general disorders (chest tightness) (Saokaew et al., 2011). Additionally, a case report from Vietnam showed that *T. crispa* promoted hepatitis in a 49-year-old man (Langrand et al., 2014). Previous studies used general and specific toxicity to assess these selected plants. Toxicological assessments of *O. aristatus* and *A. paniculata* showed no toxicity effects. Meanwhile, other plants showed slight toxicity signs. Several tissues or organs became the targets of toxicities, including testis, liver, kidney, embryo, and toxicity on brine shrimp.

Clinical trials are a small step in drug discovery and development after determining the efficacy of phytochemicals in preclinical trials (Steinmetz and Spack, 2009; L. Zhang et al., 2020). Several requirements of new compounds before being tested in clinical trials are stable compounds, simple preparation, nontoxic, interaction possibilities with other substances and foods, and others (Andrade et al., 2016). There are four phases in the clinical trials, *i.e.*, phase I (toxicity and side effects), phase II (dose-response), phase III (comparison with established treatment or placebo), and phase IV (post-marketing studies) (Skovlund and Tveit, 2015). *Syzygium cumini* is the highest number of clinical trial reports among selected diabetic medicinal plants in this study (Table 3). This plant was tested in healthy subjects and DM patients with numerous forms, such as powders, decoction of teas, extracts, products, and combinations with other plants. Nowadays, several assessments of active compounds are required to enhance the effectiveness and consistency of the antidiabetic of *S. cumini* in clinical applications. This information includes solubility, bioavailability, stability at physiological pH, and metabolism rate.

Comprehensive discussions are needed to emphasize the triangular relationship among traditional/ ethnopharmacological uses, phytochemicals, and pharmacological activities. All selected medicinal plants were tested in preclinical trials. *Andrographis paniculata* and *A. catechu* were the highest the lowest number of publications on antidiabetic mechanisms, respectively. Research trends of *A. paniculata* on antidiabetic activities have been studied in different mechanisms of action in specific periods (Arifah et al., 2021). Besides that, *A. catechu* is a well-known broad of other pharmacological activities, such as antimicrobial, anticancer, neurological effect, digestive system effect, cardiovascular effects, and others (Peng et al., 2015; Salehi et al., 2020). Furthermore, traditional use preparations also have a relationship with phytochemicals compounds, thus influencing pharmacological activities. Different preparation methods (fresh/

dried plant materials, extraction methods, solvents, and other aspects) impaired different phytochemicals and pharmacological effects (Dhanani et al., 2017; Pramono et al., 2018). So, this study is promising to develop, especially antidiabetic activities.

5. Conclusion

Ethnopharmacological surveys in Indonesia revealed 229 medicinal plants that can lower blood glucose. Almost all Indonesian provinces were surveyed, but the related ethnopharmacological databases still require enhancement. Ethnopharmacological questions (for example, plant material conditions (fresh or dried plants), plant maturity, duration of preparation, dosage, and usage duration of medicinal plants) are required to improve the comprehensiveness of the dataset to enhance the quality of future experimental design of preclinical experiments, formulations, and clinical trials. Additionally, the pharmacological activities of medicinal plants as antidiabetic should be validated at the molecular level of mechanisms of action and their complications. Active phytochemical compounds used to treat DM, their interaction with other herbals, nutritionals, and drugs, toxicity assessments, formulation studies, and clinical trials should be explored. In conclusion, this study provides primary data for plant species that are potentially antidiabetic agents and promotes local indigenous knowledge from Indonesia to the world. Further research on these plants can lead to the development of novel therapy for DM treatment, thereby promoting herbal product development and clinical application.

Funding

This work was supported by the Ministry of Research and Technology/ National Agency for Research and Innovation (RISTEK-BRIN) of the Republic of Indonesia [grant number 4953/UN1/DITLIT/DITLIT/PT/2020] through scheme of the research project of *Pendidikan Magister Menuju Doktor untuk Sarjana Unggul* (PMDSU).

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

CRediT authorship contribution statement

Fitriana Hayyu Arifah: Conceptualization, Methodology, Data curation, Writing – original draft, Writing – review & editing, Project administration. **Agung Endro Nugroho:** Supervision, Funding acquisition, Writing – review & editing. **Abdul Rohman:** Supervision, Writing – review & editing. **Wawan Sujarwo:** Supervision, Writing – review & editing.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.sajb.2022.06.042.

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