



Australian tropical medicinal plants and their phytochemicals with wound healing and antidiabetic properties

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Abstract Diabetes remains a global health challenge, with increasing numbers of patients diagnosed annually. Managing diabetes, particularly type two diabetes (T2D), requires a healthy lifestyle and medication to prevent further complications. New and effective antidiabetic drugs derived from natural products, including medicinal plants, are urgently needed because of the undesirable side effects associated with current antidiabetic drugs. Australian Aboriginal people possess rich traditional knowledge of plants used for food and therapeutic purposes. Here, we reviewed the literature on Aboriginal medicinal plants and found that a total of 126 Australian tropical plant species belonging to 47 families and 88 genera were reported as being used for treating wounds and diabetes-related conditions. We found that 28 of these

126 species were edible, of which fruits were the most consumed part. Among the 126 species, crude extracts from 29 species have been tested for their antidiabetic properties, and crude extracts of *Syzygium cumini* and *Morinda citrifolia* were the most extensively studied. Crude extracts from some species (e.g., *Morinda citrifolia*, *Eleocharis dulcis*, and *Brassica rapa*) have also been clinically evaluated in diabetic patients. Additionally, among 29 species, 374 pure compounds were isolated from 26 species. From the 374 isolated compounds, 51 have already been tested, out of which 16 were identified as antidiabetic drug leads. A total of 73 Aboriginal medicinal plants have not been tested for their phytochemical content or antidiabetic activity. These plants not only present potential targets for the biodiscovery of novel antidiabetic drug leads but also for the development of antidiabetic nutraceuticals based on traditional bush food knowledge.

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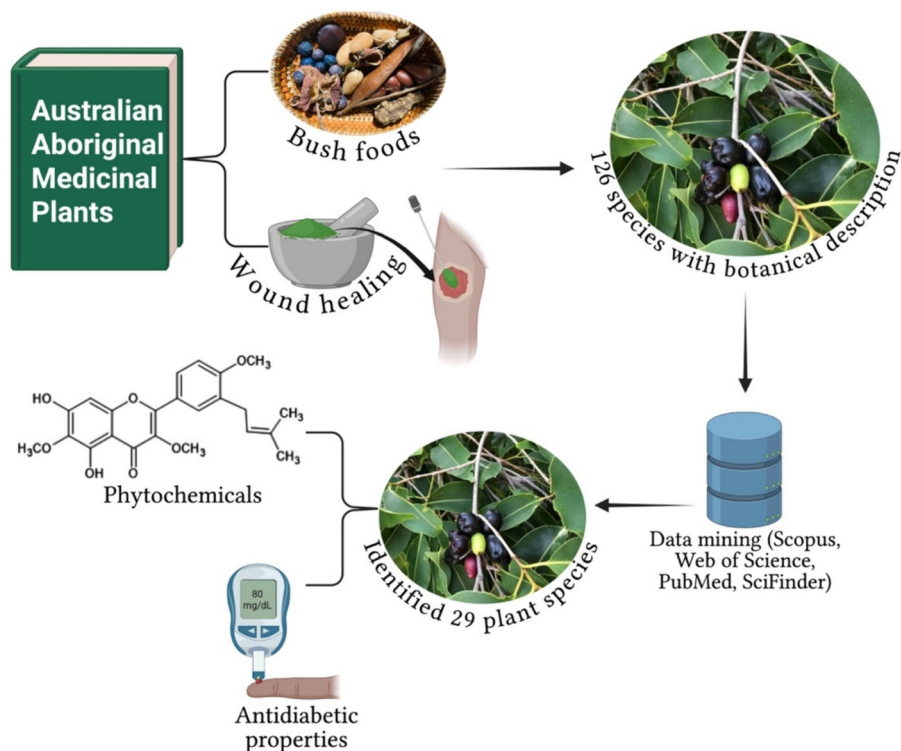
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Graphical abstract



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Introduction

Diabetes is a chronic metabolic disorder characterised by hyperglycemia, which may lead to damage to various organs, including the kidneys, nerves, eyes, heart, and blood vessels (WHO 2024). Diabetes is diagnosed as either type 1 or type 2 diabetes (T2D). Type 1 diabetes (T1D) occurs because of a complete lack of insulin, which occurs when pancreatic beta cells are destroyed. This destruction is due to genetic factors influenced by viral infections and autoimmune diseases (Ikegami et al. 2021). T1D is characterised by hyperglycemic conditions and weight loss because of increased lipolysis and protein breakdown. This type typically occurs in young people and requires insulin supplements (Ikegami et al. 2021; Lega and Lipscombe 2020). On the other hand, T2D mainly occurs in overweight people who develop insulin resistance or relative insulin deficiency (WHO 2024; Galicia-Garcia et al. 2020). Insulin insensitivity is triggered by obesity due to genetic disposition and an imbalance in energy uptake and expenditure, which increase the

fatty acid concentration in the blood. This condition reduces glucose utilisation in muscle and fatty tissues, resulting in insulin resistance and increased insulin secretion (Silbernagl et al. 2016; Jameson 2010).

The International Diabetes Federation (IDF) reported that approximately 537 million adults aged 20–79 years were diagnosed with severe diabetes in 2021 (IDF 2021), 90% of whom had T2D (Henning 2018; WHO 2024). On the basis of the current incidence rate, the number of diabetes cases is projected to increase to 643 million by 2030 and 783 million by 2045, with the highest prevalence in low- to middle-income countries, which are projected to constitute 3 in 4 adults with diabetes (IDF 2021). China and India are the top countries, with 140.9 and 74.2 million people with diabetes, respectively, in 2021 (Sun et al. 2022; IDF 2021). In Australia, 1.4 million people were living with diabetes in 2021 (AIHW 2024). The high prevalence of T2D is driven mainly by physical inactivity and energy-dense diets, leading to obesity and an aging population (WHO 2024; Chatterjee et al. 2017). These conditions cause hyperglycemia and insulin resistance, leading to diabetes complications such as cardiovascular diseases (Ali et al. 2022; Galicia-Garcia et al. 2020). In 2023, T2D was responsible for approximately 124,000 years of healthy life lost and contributed 2.2% to the total disease burden in Australia, and it was the 11th leading cause of disease burden (AIHW 2024). Diabetes is not only a global health problem but also a major economic burden. The global cost of diabetes in 2021 was estimated to be US\$966 billion (11.5% of the global health expenditure) (IDF 2021). For example, Australia's healthcare and productivity losses associated with managing T2D (along with cardiovascular diseases) are estimated to be AU\$ 421.15 and AU\$ 577.04 billion, respectively, between 2020 and 2030 (Abushanab et al. 2022; Henning 2018).

There is still no cure for T2D, and it can be managed only through a healthy lifestyle, diet, and medication with various antidiabetic drugs (WHO 2024; Tan et al. 2019). Most currently available antidiabetic drugs, including metformin (the frontline drug for T2D), help regulate blood glucose concentration/level (glycaemic control) by triggering more insulin release from the pancreas and increasing urinary glucose excretion (Tan et al. 2019; Scheen 2020; Wilson 2010). Despite their therapeutic benefits,

most antidiabetic drugs have side effects (Ali et al. 2022; Xu et al. 2018). For example, metformin can effectively lower blood glucose concentrations, but it is linked to vitamin B12 deficiency and is not recommended for patients with moderate to severe chronic kidney disease (Chatterjee et al. 2017; Tan et al. 2019). Sodium-glucose cotransporter 2 (SGLT2) inhibitor drugs are implicated in diabetic ketosis, kidney problems, and urinary tract and genital infections (Mashraqi et al. 2021). Glucagon-like peptide-1 (GLP-1) receptor agonist drugs cause gastrointestinal effects such as nausea, vomiting, diarrhoea, and constipation (Wharton et al. 2022). Thus, there is a strong demand for new and safer antidiabetic drugs (Jugran et al. 2021; Ali et al. 2015).

Antidiabetic compounds from plants often show greater efficacy with fewer side effects than synthetic drugs do (Wasana et al. 2021; Arulselvan et al. 2014), and most of these compounds have been isolated on the basis of traditional knowledge. Plant-based formulations (derived from traditional medicine knowledge) have long been used to manage diabetes and diabetes-related conditions. Australian Aboriginal people have used plants for food and therapeutic purposes for thousands of years, accumulating vast knowledge of the properties of these plants (Cribb and Cribb 1981; Barr et al. 1993). Aboriginal people have been called “food gatherers” because of their ability to sustain themselves and acquire the most intricate skills to meet the challenges of nature (Low 1989). Many plants are used to treat diabetes-related conditions, such as cuts, sores, boils, burns (DiabetesAustralia 2024), and digestive disorders (Mapp 1986), with decoctions, ointments, and infusions prepared from different parts of the plants (Clarke 2007; Williams 2010). In addition, indigenous people are aware of variations in the active components associated with soil type (Lassak and McCarthy 2011). Given that impaired wound healing is one of the major complications associated with diabetes (Chen et al. 2024; Stachura et al. 2022; Dubey et al. 2022), we hypothesised that the Aboriginal medicinal plants used to treat wounds or cuts could be potential sources of antidiabetic drug leads.

Therefore, the main aim of this review was to evaluate the antidiabetic or wound-healing properties, or efficacy of crude extracts, fractions, and isolated pure compounds reported from Aboriginal tropical medicinal plants in Australia. This review also aimed

to compile phytochemical and antidiabetic activity profiles of those medicinal plants that have already been studied as a knowledge database to support the traditional use of Aboriginal medicinal plants.

Literature review method

Figure 1 presents an overview of the strategy applied in this review. Initially, data for 149 plant species were retrieved from various books on Aboriginal medicinal plants, bush foods, and bush medicines across Australia (Cribb and Cribb 1981; Barr et al. 1993; Low 1989, 1990; Clarke 2007; Kyriaziz 1995; Williams 2010; Lassak and McCarthy 2011; Bindon 1996; Maiden 1889; Edgar et al. 1997; Webb 1959). These 149 medicinal plants were used by Australian Aboriginal people to treat diabetes-related conditions. Five datasets were further examined, namely, the Atlas of Living Australia (ALA) for plant descriptions (ALA 2024), the Australasian Virtual Herbarium (AVH) for plant distributions (AVH 2024), the World Flora Online (WFO) Plant (WFO 2024) and the Australian Plant Census (APC) for taxonomy (APC 2024), and the Useful Tropical Plants (UTP) database (UTP 2024) for additional information, including habits, parts used, and ethnomedicinal uses. The following hits were excluded: poisonous plants (5 species), plants outside the Australian Tropical Regions (5 species), and data that were not incorporated under the current plant name (13 species). The 126 species were further reviewed via online databases, such as Scopus, PubMed, Web of Science, and SciFinder, which use plant names and relevant keywords such as ‘antidiabetic,’ ‘diabetes,’ ‘isolated compounds,’ ‘crude extract,’ and ‘antidiabetic compounds.’

Results and discussion

Traditional wound-healing medicinal plants with antidiabetic potential

The Aboriginal tropical medicinal plants reviewed here were chosen for their traditional use in wound healing, as terms like ‘hyperglycemia’ were not used in ancient times. Today, it is well established that glucose metabolism is essential for wound healing, providing the energy required for cellular and tissue

repair (Demling 2009; Eming et al. 2021; Im and Hoopes 1970). However, in diabetic patients, impaired glucose regulation leads to chronic wounds and delayed healing (Patel et al. 2019). This disruption in normal wound repair process is driven by factors such as persistent hyperglycemia, nerve damage, and vascular complications, which can result in infections, ulcers, and even limb amputation (Falanga 2005; Brem and Tomic-Canic 2007).

Modern therapeutic strategies for diabetes, including dipeptidyl peptidase-4 (DPP-4) inhibitors and metformin, have shown promise in supporting wound healing (Spampinato et al. 2020; Han et al. 2017). Additionally, natural compounds like betulinic acid have been found to accelerate diabetic wound healing by reducing inflammation and oxidative stress (Yadav et al. 2024). These findings highlight a significant link between the wound healing effects of medicinal plants and their antidiabetic properties (Oguntibeju 2019). Several medicinal plants traditionally used for wound healing have also exhibited antidiabetic effects, suggesting a valuable dual therapeutic potential. For instance, *Aloe vera* leaf has been widely applied in traditional medicine for treating burns and skin injuries, and studies have confirmed its role in glycemic control and improving insulin sensitivity in diabetic models (Adamu et al. 2021). *Azadirachta indica* (commonly known as neem) is another example. It is commonly used for its antimicrobial and wound-healing properties, and also shown to exert hypoglycemic effects in both animal and clinical studies (Rafe 2017). Similarly, seeds of *Trigonella foenum-graecum* (Fenugreek), traditionally used in wound poultices, have demonstrated antidiabetic activity through delayed glucose absorption and improved insulin function (Bharathy and Thanikachalam 2024).

Australian tropical medicinal plants with antidiabetic properties

In Australia, more than 500 species of native plants have been documented for their medicinal uses, highlighting the country’s rich biodiversity and the rich traditional biocultural knowledge held by indigenous communities (Cribb and Cribb 1981). Many of these plants have been used to treat a range of ailments, including metabolic disorders. Our review led to the identification of 126 medicinal plants (Fig. 1) that are traditionally used by Aboriginal people to treat

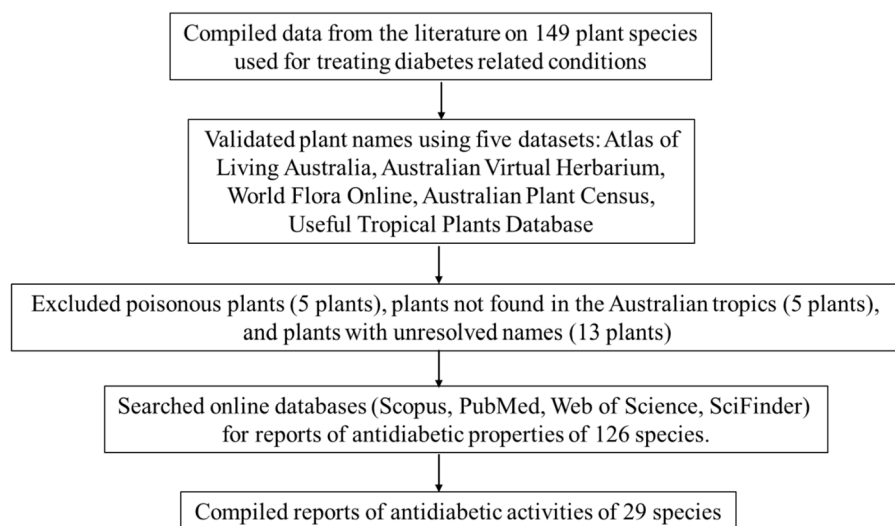


Fig. 1 Overview of strategies applied to review and select antidiabetic medicinal plants used by Aboriginal people in Australia

diabetes-related conditions, such as wounds, ulcers and digestive disorders (Table 1 & 2). Among the 126 species, 29 have been studied for their antidiabetic properties, 26 have been studied both for their antidiabetic and phytochemical properties (Table 1), and 73 species have not been reported for their antidiabetic activities or isolated compounds (Table 2).

Diversity and habit of antidiabetic medicinal plants

The 126 selected medicinal plants (Tables 1, 2) belong to 47 families and 88 genera. Myrtaceae was the dominant family (with 17 species), followed by Fabaceae (14 species), Euphorbiaceae (11 species), and Malvaceae, Proteaceae and Lamiaceae (6 species each) (Fig. 2). With more than 6,000 species, Myrtaceae is found mainly in tropical regions and has been exploited for human use (Hardstaff et al. 2022). Some genera of Myrtaceae that have medicinal purposes are *Eucalyptus*, *Eugenia*, *Melaleuca*, and *Syzygium*. Among the *Syzygium* species, *Syzygium cumini* is known for its antidiabetic properties (Masaenah et al. 2021). This species has thus been studied for its constituents. Other species of the genera *Eucalyptus*, *Eugenia*, and *Melaleuca* have not been reported to have antidiabetic properties.

Shrubs were the most dominant lifeform (54 species), followed by trees (45 species), herbs (18 species), climbers (7 species), epiphytes (2 species), and palm-like plants (1 species) (Fig. 3A). An

example of a medicinal shrub is *Melastoma affine* (Melastomataceae), a pioneer shrub species in the rainforests of Australasian rainforests, including those in India, China, Papua New Guinea, Southeast Asia, and Australia (Gross 1993; AVH 2024). An example of a medicinal tree is *Melaleuca leucadendra*, and an example of a medicinal herb is *Cleome viscosa*, whose leaves and young shoots are edible and are used to heal wounds and ulcers (Lassak and McCarthy 2011).

Different parts of the antidiabetic medicinal plants used for treatment

Various parts of plants are indicated as medicinal by the Australian Aboriginal people to treat diabetes-related symptoms, and they are classified into eight categories: 'whole plant,' 'leaf,' 'bark,' 'root,' 'plant exudate,' 'fruit and seed,' 'charcoal and ash,' and 'twig' (Fig. 3B). The 'whole plant' category refers to herbaceous plants where the roots, stems, and leaves are easier to collect than specific parts. The 'leaf' category comprises young leaves, leaf stalks, petioles, and young shoots; the 'bark' category includes outer and inner bark and root bark; the 'root' category includes tap roots, tubers, and bulbs; the 'plant exudate' category includes sap, gum, resin, kinos, and latex; and the 'fruit and seed' category comprises fruits, seeds, kernels, and pods. Leaves were the most commonly used part (38.8%), followed by bark (16.3%), fruit and seeds (11.8%), whole plants (10.7%), plant exudates (10.1%), roots (8.4%), charcoal and ash

Table 1 Australian tropical medicinal plants traditionally used for treating wounds and diabetes-related conditions that are studied for phytochemical composition and/or antidiabetic properties (Cribb and Cribb 1981; Barr et al. 1993; Low

1989, 1990; Clarke 2007; Kyriaziz 1995; Williams 2010; Lassak and McCarthy 2011; Bindon 1996; Maiden 1889; Edgar et al. 1997; Webb 1959; ALA 2024; AVH 2024; APC 2024; WFO 2024; UTP 2024)

Family	Botanical name	Habit	Part(s) used	Conditions or ailments treated	Phytochemical studies/compound isolation	Antidiabetic studies
Acanthaceae	<i>Avicennia marina</i> (Forssk.) Vierh.	Tree	Leaves, young shoots, ash, and charcoal of wood	Pain relief, skin lesions and infections, ulcers, sores	Yes	Yes
Apocynaceae	<i>Cynanchum viminalis</i> subsp. <i>australe</i> (R.Br.) Meve & Liedtke	Shrub	Sap	Bleeding wounds and healing sores	Yes	No
Asteraceae	<i>Ageratum conyzoides</i> L.	Herb	Whole plant	Wounds	Yes	Yes
	<i>Pterocaulon serrulatum</i> (Montrouz.) Guillaumin	Herb	Whole plant	Wounds	Yes	No
	<i>Pterocaulon sphacelatum</i> (Labill.) Benth. & Hook.f. ex F.Muell.	Shrub	Leaves	Open wounds, sores, and inflamed eyes	Yes	No
Boraginaceae	<i>Heliotropium indicum</i> L.	Herb	Leaves	Skin sores and rheumatism	Yes	Yes
Capparaceae	<i>Capparis lanceolaris</i> DC.	Shrub	Bark	Scratches and sores	Yes	No
Cleomaceae	<i>Cleome viscosa</i> L.	Herb	Leaves, young shoots (edible)	Counterirritant, wounds, ulcers, and earache	Yes	Yes
Combretaceae	<i>Terminalia catappa</i> L.	Tree	Leaves (fruits are edible)	Mouth infections and sore throat	Yes	Yes
Convolvulaceae	<i>Ipomoea pes-caprae</i> (L.) R.Br.	Climber	Leaves	Boils, salves, sexually transmitted disease, sores	Yes	No
	<i>Merremia tridentata</i> (L.) Hallier f.	Climber	Whole plant	Sores, skin lesions, wounds	Yes	Yes
Cyperaceae	<i>Eleocharis dulcis</i> (Burm.f.) Trin. ex Hensch	Shrub	Whole plant (tubers are edible)	Wounds	Yes	Yes

Table 1 continued

Family	Botanical name	Habit	Part(s) used	Conditions or ailments treated	Phytochemical studies/compound isolation	Antidiabetic studies
Euphorbiaceae	<i>Acalypha wilkesiana</i> Müll.Arg.	Shrub	Whole plant	Open sores, sedative	Yes	Yes
Fabaceae	<i>Euphorbia atoto</i> G.Forst.	Shrub	Milky sap	Ulcers	Yes	No
	<i>Euphorbia pilulifera</i> L.	Herb	Leaves. Leaves are also consumed as herbal tea	Pain relief, wounds	Yes	No
	<i>Macaranga tanarius</i> (L.) Müll.Arg.	Shrub	Leaves	Wounds	Yes	Yes
	<i>Acacia auriculiformis</i> A.Cunn. ex Benth.	Tree	Whole plant	Sores, sore eyes, aches, rheumatism, allergy, itching, rashes	Yes	Yes
	<i>Acacia kempeana</i> F.Muell.	Shrub	Leaves	Wounds	No	Yes
	<i>Castanospermum australe</i> A.Cunn. ex Mudie	Tree	Seeds (edible)	Postprandial hyperglycaemia in diabetic patients	Yes	Yes
Flagellariaceae	<i>Flagellaria indica</i> L.	Climber	Leaves	Wound healing, sore eyes	No	Yes
Hydrophyllaceae	<i>Hydrolea zeylanica</i> (L.) Vahl	Herb	Leaves (young shoots are edible)	Ulcers, wounds	No	Yes
Lamiaceae	<i>Ajuga australis</i> R.Br.	Shrub	Leaves	Wounds, ulcers, sores	Yes	No
	<i>Ocimum gratissimum</i> L.	Herb	Whole plant	Hypotension	Yes	Yes
	<i>Ocimum tenuiflorum</i> L.	Shrub	Whole plant	Diarrhoea, dysentery, malaria, skin disease, wounds	Yes	Yes
	<i>Volkameria inermis</i> L.	Shrub	Leaves, bark	Sores, wounds	Yes	Yes
Lauraceae	<i>Cassytha filiformis</i> L.	Climber, parasite	Whole plant	Ulcers, inflamed eyes	Yes	Yes
Lecythidaceae	<i>Planchonia careya</i> (F.Muell.) R.Knuth	Tree	Bark (fruits are edible)	Wounds, sores	Yes	No
Loganiaceae	<i>Strychnos lucida</i> R.Br.	Shrub	Bark, roots, fruits	Skin sores, burns, cuts, wounds	Yes	No

Table 1 continued

Family	Botanical name	Habit	Part(s) used	Conditions or ailments treated	Phytochemical studies/compound isolation	Antidiabetic studies
Malvaceae	<i>Abutilon indicum</i> (L.) Sweet	Shrub	Whole plant	Leprosy, ulcers. It also possesses demulcent properties and anti-inflammatory properties	Yes	Yes
	<i>Grewia hirsuta</i> Vahl	Shrub	Roots	Cuts, sores	Yes	Yes
	<i>Hibiscus vitifolius</i> L.	Herb	Roots or tubers	Boils	Yes	Yes
Melastomataceae	<i>Melastoma affine</i> D.Don	Shrub	Leaves (fruits are edible)	Diarrhoea, dysentery, burns, ulcers, and wounds	Yes	Yes
Menispermaceae	<i>Tinospora smilacina</i> Benth.	Climber	Whole plant	Pain relief, headache, rheumatism, wounds	Yes	No
Moraceae	<i>Ficus coronata</i> Spin	Tree	Leaves (syconia are edible)	Wounds	Yes	No
	<i>Ficus racemosa</i> L.	Shrub	Bark, leaves (syconia are a bush food)	Boils	Yes	Yes
Myoporaceae	<i>Eremophila duttonii</i> F.Muell.	Shrub	Leaves	Infected cuts, scabies, open sores, ears, inflamed eyes	Yes	No
Myrtaceae	<i>Eucalyptus camaldulensis</i> Dehnh.	Tree	Leaves	Wounds and sores	Yes	No
	<i>Eucalyptus microtheca</i> F.Muell.	Tree	Leaves (seeds are edible)	Skin sores	Yes	No
	<i>Melaleuca leucadendra</i> (L.) L.	Tree	Leaves, bark (flowers used for making sweet drinks)	Sedative, respiratory infections, skin diseases	Yes	No
	<i>Syzygium cumini</i> (L.) Skeels	Tree	Leaves (fruits are edible)	Diabetes	Yes	Yes
Orchidaceae	<i>Cymbidium sp.</i>	Herb	Leaves	Cuts, sores, and burns	Yes	No
Pandanaceae	<i>Pandanus tectorius</i> Parkinson	Tree	Leaves, stems (fruits and kernels are edible)	Cold/flu, hepatitis, dysuria, asthma, boils, cancer, and to alleviate vomiting	Yes	Yes
Phyllanthaceae	<i>Flueggea virosa</i> (Roxb.ex Willd.) Royle	Shrub	Whole plant (fruits are edible)	Sores and skin ailments	Yes	No
Poaceae	<i>Cymbopogon ambiguus</i> (Hack.) A.Camus	Shrub	Leaves	Wounds and sores	Yes	No
Proteaceae	<i>Grevillea striata</i> R.Br.	Shrub	Charcoal of plant, and dried sap from bark	Wounds	Yes	No

Table 1 continued

Family	Botanical name	Habit	Part(s) used	Conditions or ailments treated	Phytochemical studies/compound isolation	Antidiabetic studies
Rhamnaceae	<i>Ventilago viminalis</i> Hook.	Climber	Bark, roots	Toothache, rheumatism, swelling, cuts, sores	Yes	No
	<i>Ziziphus oenopolia</i> (L.) Mill.	Shrub	Whole plant	Fresh wounds, ulcers	Yes	Yes
Rubiaceae	<i>Morinda citrifolia</i> L.	Tree	Leaves	Wounds, ulcers	Yes	Yes
Sapindaceae	<i>Dodonaea polyandra</i> Merr. & L.M.Perry	Tree	Leaves and roots	Pain relief, toothache, cuts, open wounds	Yes	No
	<i>Dodonaea viscosa</i> Jacq.	Shrub	Leaves	Open cuts and wounds	Yes	Yes
Scrophulariaceae	<i>Eremophila sturtii</i> R.Br.	Shrub	Leaves	Sores, cuts	Yes	No
Simaroubaceae	<i>Brucea javanica</i> (L.) Merr.	Tree	Leaves, roots, and seeds	Dysentery, malaria, pain relief	Yes	Yes
Verbenaceae	<i>Verbena officinalis</i> L.	Herb	Whole plant	Wounds	Yes	No

(2.2%), and twigs (1.7%). The ease of collection, availability, and minimisation of plant damage facilitate the frequent use of leaves (Turpin et al. 2022).

Disease categories and methods of treatment preparations

We grouped the diseases or conditions associated with the 126 identified medicinal plants into nine categories (Fig. 4). Among the nine categories, the ‘skin sores and infections’ (34%), ‘cuts, wounds, and burns’ (32%), and ‘boils and ulcers’ (9%) categories were associated with mostly treated diseases. For example, dried and powdered sap collected from damaged areas of *Grevillea striata* bark is sprinkled onto sores, burns, and cuts as a drying agent (Cribb and Cribb 1981). The leaves and twigs of *Acacia translucens* are mashed in water, and the liquid is used to bathe skin sores; a leaf decoction of *Ipomoea pes-caprae* is applied to sores, scabies, bites, and stings (Lassak and McCarthy 2011). ‘Toothache and mouthwash’ (3%), ‘anti-inflammatory’ (3%), ‘rheumatism’ (3%), and ‘digestive disorder’ (diarrhoea and vomiting, 2%) were the least commonly treated diseases or conditions. The ‘others’ category includes dysentery, malaria, respiratory infection, cold

and flu, hepatitis, scabies, sexually transmitted infections (STIs), sedatives, and immune system boosters.

Typically, plant parts were prepared in different forms before application or consumption to treat diseases or conditions. They most commonly prepared decoctions or infusions, chew paste, charcoal, and ash or directly applied fresh materials (Lassak and McCarthy 2011; Williams 2010, 2021; Fern 2014). For example, sap collected from damaged areas of *Grevillea striata* bark is dried and powdered to apply on sores, burns, and cuts as a drying agent (Cribb and Cribb 1981). The leaves, bark, and roots of *Alphitonia excelsa* are mashed or crushed and made into aqueous decoctions or infusions before being applied to wounds or sores (Cribb and Cribb 1981; Lassak and McCarthy 2011). A similar method was applied to the leaves of *Brachychiton diversifolius*, *Pterocaulon sphacelatum*, and *Acacia kempeana* and the bark and roots of *Buchanania arborescens*, *Capparis lanceolaris*, and *Grewia retusifolia* (Lassak and McCarthy 2011; Maiden 1889; Barr et al. 1993). Some plants were prepared by boiling or heating them with seawater or saltwater, such as the inner bark of *Hibiscus tiliaceus* and the whole plant of *Eleocharis dulcis* (Cribb and Cribb 1981; Lassak and McCarthy 2011; Fern 2014).

Table 2 Australian tropical medicinal plants traditionally used for treating wounds and diabetes-related conditions not studied for phytochemical composition and antidiabetic properties (Cribb and Cribb 1981; Barr et al. 1993; Low 1989, 1990;

Clarke 2007; Kyriaziz 1995; Williams 2010; Lassak and McCarthy 2011; Bindon 1996; Maiden 1889; Edgar et al. 1997; Webb 1959; ALA 2024; AVH 2024; APC 2024; WFO 2024; UTP 2024)

Family	Botanical name	Habit	Part(s) used	Conditions or ailments treated
Amaryllidaceae	<i>Crinum arenarium</i> Herb.	Shrub	Bulbs	Wounds, sores
Anacardiaceae	<i>Buchanania arborescens</i> Blume	Tree	Inner bark, sapwood, roots (fruits are edible)	Toothache, mouthwash
	<i>Buchanania obovata</i> Engl.	Tree	Leaves, fruit, bark, sapwood (fruits are edible)	Mouthwash, sore eyes, infected rashes, scabies, skin ulcers
	<i>Semecarpus australiensis</i> Engl.	Tree	Leaves (nuts are edible)	Rheumatism, swellings and redness of skin (allergic reactions)
Apocynaceae	<i>Alstonia actinophylla</i> K.Schum.	Tree	Leaves, milky sap	Wounds, sores
	<i>Secamone elliptica</i> R.Br.	Climber	Leaves, stems, milky sap	Wounds
Asteraceae	<i>Cymbonotus lawsonianus</i> Gaudich.	Shrub	Leaves	Wounds
Boraginaceae	<i>Trichodesma zeylanicum</i> (Burm.f.) R.Br.	Herb or Shrub	Leaves, roots	Wounds, pain relief
Burseraceae	<i>Canarium muelleri</i> F.M.Bailey	Tree	Resin	Cuts, sores, chronic ulcers
Combretaceae	<i>Terminalia hadleyana</i> W.Fitzg.	Shrub	Leaves (fruits are edible)	Skin sores
	<i>Terminalia muelleri</i> Benth.	Tree	Leaves	Skin sores, scabies
Cupressaceae	<i>Callitris columellaris</i> F.Muell.	Tree	Bark, leaves, twigs	Abdominal pain and diarrhoea, sores, cuts
Cycadaceae	<i>Cycas armstrongii</i> Miq.	Palm-like	Leaves, stems, seeds	Wounds
Dilleniaceae	<i>Dillenia alata</i> (R.Br. ex DC.) Banks ex Martelli	Tree	Leaves	Wounds, sores
Euphorbiaceae	<i>Croton arnhemicus</i> Müll.Arg.	Shrub	Inner bark	Headache, infected cuts, skin rashes and sores
	<i>Euphorbia australis</i> Boiss.	Herb	Milky sap	Skin sores
	<i>Euphorbia coghlani</i> F.M.Bailey	Shrub	Milky sap	Skin sores
	<i>Excoecaria parvifolia</i> Müll.Arg.	Tree	Bark	Sores, cuts
	<i>Homalanthus populifolius</i> Graham	Shrub	Leaves	Wounds and cuts to stop bleeding
	<i>Petalostigma quadriloculare</i> F.Muell.	Shrub	Bark, fruits	Itchy skin, sores, cuts, rabies infection
	<i>Synostemon glaucus</i> F.Muell.	Shrub	Roots	Sores, cuts
	<i>Acacia ancistrocarpa</i> Maiden & Blakely	Shrub	Whole plant	Skin sores
Fabaceae	<i>Acacia estrophiolata</i> F.Muell.	Tree	Bark, roots	Sores, boils, scabies, headache, stomach pain, wounds, burns
	<i>Acacia inaequilatera</i> Domin	Shrub	Bark	Skin sores, cuts, rashes. It has an astringent and drying action
	<i>Acacia leptocarpa</i> A.Cunn. ex Benth.	Shrub	Bark, seeds (seeds are edible)	Wounds, sore eyes
	<i>Acacia pellita</i> O.Schwarz	Shrub	Leaves, seeds	Sores
	<i>Acacia translucens</i> A.Cunn. ex Hook.	Shrub	Leaves, twigs	Skin sores, headache
	<i>Bauhinia carronii</i> (F.Muell.) Pedley	Tree	Bark	Sores
	<i>Canavalia rosea</i> (Sw.) DC.	Herb	Root, leaves, and petioles. Seeds and pods are edible	Aches, pains, leprosy, and wounds
	<i>Lysiphyllum cunninghamii</i> (Benth.) de Wit	Shrub	Roots, bark	Wounds, sores
	<i>Sesbania burbridgeae</i> C.L.Gross	Tree	Leaves	Boils
	<i>Sesbania formosa</i> (F.Muell.) N.T.Burb.	Tree	Bark ash (flowers are edible)	Wounds, sores

Table 2 continued

Family	Botanical name	Habit	Part(s) used	Conditions or ailments treated
Goodeniaceae	<i>Scaevola taccada</i> (Gaertn.) Roxb.	Shrub	Leaves, bark	Wounds
	<i>Goodenia ovata</i> Sm.	Shrub	Leaves, twigs	Diabetes
Gyrostemonaceae	<i>Codonocarpus cotinifolius</i> (Desf.) F.Muell.	Shrub	Leaves, stems	Sores, cuts
Lamiaceae	<i>Orthosiphon aristatus</i> (Blume) Miq.	Herb	Whole plant	Diuretic and antihypertensive
	<i>Pityrodia jamesii</i> Specht	Shrub	Leaves	Wounds, sores
Loranthaceae	<i>Decaishina brittenii</i> (Blakely) Barlow	Epiphyte	Whole plant	Wounds, sores
Malvaceae	<i>Grewia latifolia</i> F.Muell. ex Benth.	Shrub	Leaves (fruits are edible)	Dysentery, toothache, boils, sores
	<i>Grewia retusifolia</i> Kurz	Shrub	Leaves, roots, bark (fruits are edible)	Wounds, sores, diarrhoea
	<i>Hibiscus tiliaceus</i> L. subsp. <i>tiliaceus</i>	Shrub	Inner bark and sapwood	Wounds
Meliaceae	<i>Owenia vernicosa</i> F.Muell.	Tree	Bark	Skin sores, open cuts, infected eyes
Moraceae	<i>Ficus coronulata</i> Miq.	Tree	Leaves, milky sap of young shoots (bush food)	Sores, cuts
	<i>Ficus opposita</i> Miq.	Shrub	Leaves (bush food)	Bruises, swellings, rheumatism, sores
Myrtaceae	<i>Calytrix exstipulata</i> DC.	Shrub	Leaves	Wounds, sores
	<i>Corymbia papuana</i> (F.Muell.) K.D.Hill & L.A.S.Johnson	Tree	Bark, resin	Wounds, sores
	<i>Corymbia ptychocarpa</i> (F.Muell.) K.D.Hill & L.A.S.Johnson	Tree	Leaves	Wounds, sores
	<i>Corymbia terminalis</i> (F.Muell.) K.D.Hill & L.A.S.Johnson	Tree	Leaves, gum from bark and trunk	Wounds, sores
	<i>Eucalyptus crebra</i> F.Muell.	Tree	Bark	Sores
	<i>Eucalyptus dichromophloia</i> (F.Muell.) K.D.Hill & L.A.S.Johnson	Tree	Leaves	Wounds, sores
	<i>Eucalyptus miniata</i> A.Cunn. ex S.Schauer	Tree	Leaves	Skin sores
	<i>Eucalyptus tetrodonta</i> F.Muell.	Tree	Leaves	Sores, cuts
	<i>Eugenia reinwardtiana</i> (Blume) DC.	Tree	Fruits (edible)	Wounds
	<i>Syzygium erythrocalyx</i> (C.T.White) B.Hyland	Tree	Fruits (edible)	Wounds
	<i>Syzygium forte</i> (F.Muell.) B.Hyland	Tree	Bark (fruits are edible)	Sore throat, bronchitis, asthma, thirst, biliousness, dysentery, ulcers
	<i>Syzygium luehmannii</i> (F.Muell.) L.A.S.Johnson	Tree	Fruits (edible)	Sore ears, wounds, skin conditions, immune system booster
	<i>Syzygium suborbiculare</i> (Benth.) T.G.Hartley & L.M.Perry	Shrub	Leaves, fruits (edible)	Chest congestion, cough, wounds, sore ear, toothache
Orchidaceae	<i>Cymbidium canaliculatum</i> R.Br.	Herb	Whole plant (fruits and stems are edible)	Wounds
	<i>Dendrobium affine</i> (Decne.) Steud.	Epiphyte	Sticky liquid from pseudobulb	Infected skin lesions, sores
	<i>Dendrobium foelschei</i> F.Muell.	Herb	Sticky liquid from pseudobulb	Infected sores, cuts
Plantaginaceae	<i>Stemodia viscosa</i> Roxb.	Herb	Leaves	Wounds
Poaceae	<i>Cymbopogon procerus</i> (R.Br.) Domin	Herb	Whole plant	Sores, cuts
Proteaceae	<i>Grevillea heliosperma</i> R.Br.	Shrub	Leaves, bark	Sores
	<i>Grevillea pyramidalis</i> A.Cunn. ex R.Br.	Shrub	Bark	Sores
	<i>Hakea arborescens</i> R.Br.	Shrub	Leaves, pods	Scabies, sores
	<i>Hakea macrocarpa</i> A.Cunn. ex R.Br.	Shrub	Charcoal from wood	Open sores, cuts
	<i>Persoonia falcata</i> R.Br.	Shrub	Leaves, bark (fruits are edible)	Diarrhoea, infection and soreness relief, wounds

Table 2 continued

Family	Botanical name	Habit	Part(s) used	Conditions or ailments treated
Rhamnaceae	<i>Alphitonia excelsa</i> (Fenzl) Benth.	Tree	Leaves, bark, roots	Sores, rashes, ringworm, headache, toothache
Rubiaceae	<i>Gardenia pyrifolia</i> A.Cunn. ex Benth.	Shrub	Bark	Aches, sores
Santalaceae	<i>Exocarpos latifolius</i> R.Br.	Tree	Leaves	Boils
	<i>Santalum lanceolatum</i> R.Br.	Tree	Leaves, roots (fruits are edible)	Wounds, sores
Sterculiaceae	<i>Brachychiton diversifolius</i> (A.Cunn. ex G.Don) F.Muell.	Tree	Leaves, gummy exudate	Wounds, sores, ulcerated skin
	<i>Sterculia quadrifida</i> R.Br.	Tree	Leaves (seeds are edible)	Sore eyes, wounds

The leaves and twigs of *Acacia translucens* are mashed in water, and the liquid is used to bathe skin sores; a leaf decoction of *Ipomoea pes-caprae* is applied to sores, scabies, bites, and stings (Lassak and McCarthy 2011). The fruit of *Grewia retusifolia* is eaten raw to cure diarrhoea and dysentery (Low 1990; UTP 2024). Chewing leaves or drinking an infusion of the mashed roots of *Grewia retusifolia* is also indicated for digestive disorders (Edgar et al. 1997). For example, an infusion of the young leaves of *Flueggea virosa* is drunk for internal pain (Edgar et al. 1997). A decoction from crushed leaves of *Melaleuca leucadendra* is taken orally to ease cough and cold (Low 1990; UTP 2024). Leaves and young shoots of *Avicennia marina* and *Dodonaea polyandra* are chewed and pulped before being applied to wounds. Plant exudates, including resin, oil, latex, and milky sap collected from bark, leaves, or trunks of *Ficus coronulata*, *Euphorbia australis*, and *Corymbia papuana* are directly applied to skin lesion burns, wounds, and cuts (Lassak and McCarthy 2011; Cribb and Cribb 1981; Low 1990). Similarly, charcoal and ash made from the wood of *Grevillea striata* and *Hakea macrocarpa* are also applied to open sores and cuts (Cribb and Cribb 1981; Lassak and McCarthy 2011; Fern 2014). In addition, the seed extracts of *Syzygium cumini* and *Brucea javanica* are considered powerful remedies for treating diabetes (Gajera et al. 2017b; Lassak and McCarthy 2011; Y. Zhan et al. 2020).

Antidiabetic medicinal plants as bush foods

Bush food includes plants, vegetables, fruits, nuts, or berries native to Australia which is used for culinary and medicinal purposes (Mathew 2016, Lawrie 2023). Among the 126 species (Tables 1 & 2), 28 were found to be consumed as bush foods by Australian

Aboriginal people. Figure 5 shows the edible plant parts, including fruits (15 species), seeds, pods, and kernels (6 species), flowers, nuts and tubers, leaves and young shoots (2 species each). Only one species was indicated for stems (Fig. 5). Fruits were the most consumed plant part and were typically eaten as raw or roasted form. Examples include the fruits of some *Syzygium* species and others, such as *Grewia retusifolia* and *Persoonia falcata*. The leaves and young shoots (e.g., *Cleome viscosa* and *Hydrolea zeylanica*) were boiled and consumed as vegetables. Young leaves and flowers from *Sesbania formosa* were eaten raw or cooked, while the flowers and leaves of *Melaleuca leucadendra* were taken as herbal tea (Lassak and McCarthy 2011). The pseudobulb (a thickened stem) of *Cymbidium canaliculatum* containing starch is eaten raw or cooked. Another example is *Pandanus tectorius*, whose seeds are consumed raw or cooked, while young flower buds and aerial roots are cooked (Edgar et al. 1997; Kyriaziz 1995; Williams 2010; Fern 2014).

Other commonly consumed parts are the seeds, pods, and kernels. They are either extracted or boiled before consumption. For example, the young pods and seeds of *Canavalia rosea* were boiled or cooked before they are eaten (Fern 2014). Seeds were important source of dietary protein and carbohydrates but can sometimes be harmful if eaten as raw. For example, fresh seeds of *Castanospermum australe*, a native plant of Australia, contain high levels of saponins (Lassak and McCarthy 2011; Fern 2014). To avoid the toxicity of saponins, seeds are finely sliced and soaked in running water for 10 days before roasting and grinding them into a powder (Fern 2014; Maiden 1889). A high content of saponins has cytotoxic activities (Jiang et al. 2018), possesses

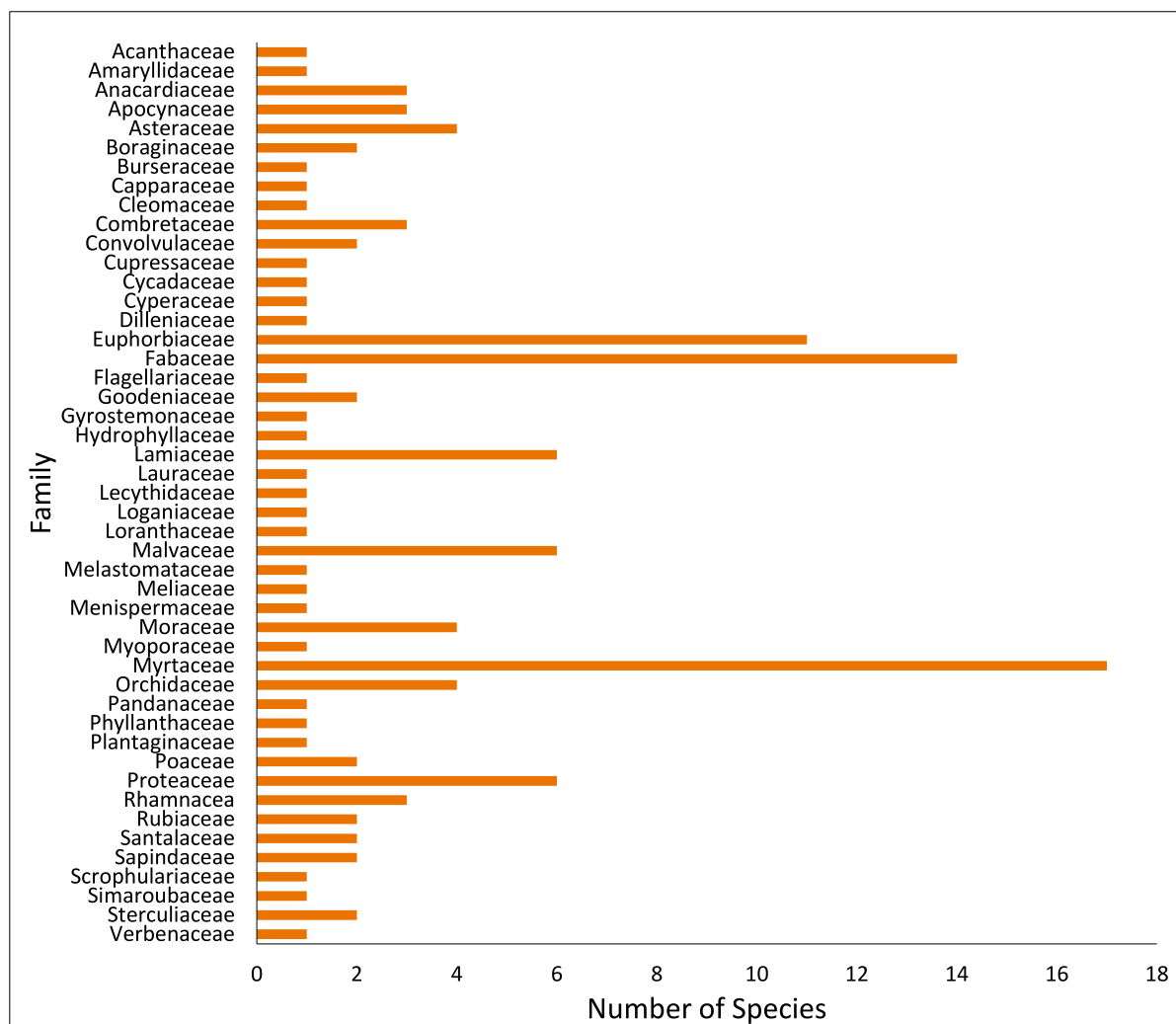


Fig. 2 Diversity of Australian tropical medicinal plants for treating diabetes-related conditions by family

harmful haemolytic toxicity (Zheng et al. 2019), and causes diarrhoea (Lin et al. 2021).

Edible medicinal plants have potential health benefits as nutraceuticals and dietary supplements, particularly for the prevention or treatment of T2D (Xu et al. 2018; Lin et al. 2024). Nutraceuticals are defined as a food or food component that provides medicinal or health benefits, including prevention and treatment of diseases (DeFelice 1995). Due to their established safety profile, nutraceuticals and dietary supplements are associated with low risks of obesity and diabetes (Zhu et al. 2020). Moreover, from a psychological perspective, regular supplementation

with consumable plants can improve patient adherence following a T2D diagnosis, as nutraceuticals are generally well received by individuals with chronic conditions (Mahmood et al. 2020; Barry 2018; Piragine et al. 2022). Furthermore, using edible plants rich in active compounds therapeutically could benefit the early stages of T2D. This approach may help slow disease progression, delay the need for synthetic antidiabetic drugs, and reduce the onset of diabetic complications (Piragine et al. 2022). In addition to their potential for lowering glucose levels, antidiabetic medicinal plants possess antioxidant and anti-inflammatory properties that may help prevent

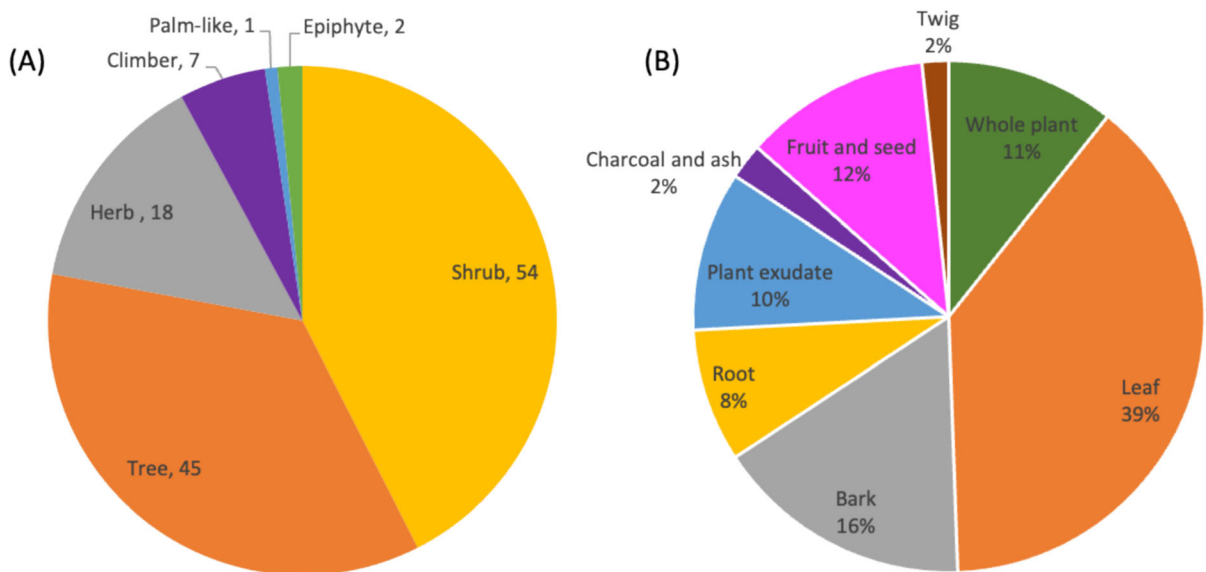


Fig. 3 Habit (A) and plant parts used (B) of Australian antidiabetic tropical medicinal plants

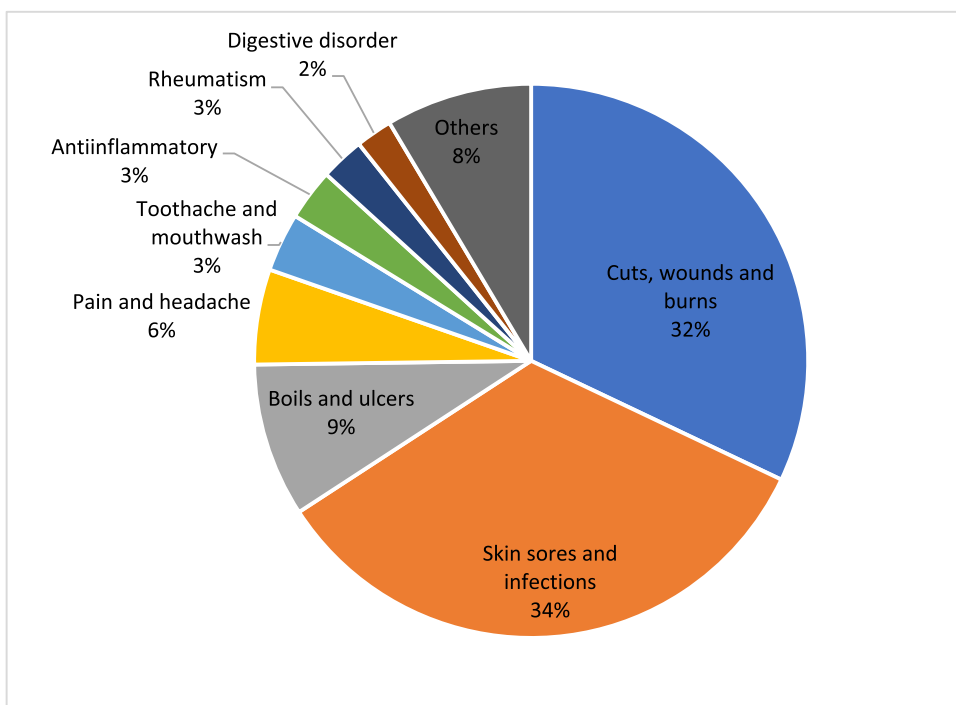


Fig. 4 Categories and percentages of diseases treated by the Australian tropical medicinal plants

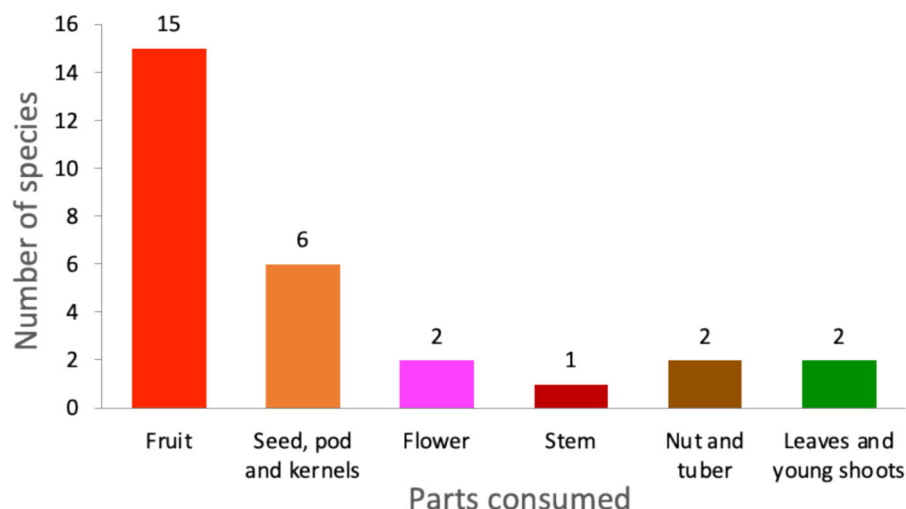


Fig. 5 Different parts of Australian tropical medicinal plants used as bush foods

microvascular and macrovascular complications related to T2D (Piragine et al. 2022; Khan et al. 2013; Subramaniam et al. 2014). Thus, interest in antidiabetic compounds or products derived from medicinal plants is increasing, as they have proven effective in managing diabetes and its complications with minimal side effects (Lin et al. 2024).

Crude extracts and phytochemicals from aboriginal medicinal plants

1. Antidiabetic crude extracts

The in vitro antidiabetic activities of plant crude extracts (Table 3) primarily rely on inhibiting two metabolic enzymes: α -glucosidase and α -amylase. These enzymes are crucial in the pathogenesis of T2D as they play key roles in glucose production and the absorption of carbohydrates during digestion. Therefore, inhibiting these enzymes is a significant strategy in managing blood glucose levels (Obloh et al. 2014; Hamden et al. 2013). Based on half-maximal inhibitory concentration (IC_{50}) values against α -glucosidase and α -amylase enzymes' activities, seed extract of *Syzygium cumini*, fruit extract of *Terminalia catappa*, and root bark extract of *Acalypha wilkesiana* were the three most promising extracts (Fitri Amelia et al. 2024, Laxman Sawant et al. 2015) (Table 3). *Syzygium cumini* seed extract inhibited α -amylase at much lower concentrations than standard acarbose (24.7 μ g/mL)

(Gajera et al. 2017b). Another enzyme inhibition test focuses on DPP-IV (Dipeptidyl peptidase-IV), which plays a significant role in glucose metabolism. Inhibiting DPP-IV can help normalize blood glucose levels in humans, making it a potential treatment for T2D (Huang et al. 2019; Florentin et al. 2022). For this activity, the seed extract of *C. australe* exhibited higher in vitro inhibitory activity (IC_{50} = 13.96 μ g/mL) of DPP-IV compared to the standard Diprotin A (IC_{50} = 1.543 μ g/mL).

From the review of crude extracts studies from 29 species (Table 3), crude extracts of *Syzygium cumini*, *Morinda citrifolia*, and *Acalypha wilkesiana* were most widely studied for their in vitro antidiabetic activities. Almost all parts of *Syzygium cumini* have been examined, demonstrating antidiabetic effects, with the leaves and seeds showing superior activities (Mahindrakar and Rathod 2022; Mujawah et al. 2023; Syama et al. 2018; Gajera et al. 2017a, Zheng et al. 2019). The leaves and root bark of *Acalypha wilkesiana* have also been investigated (Oyebode et al. 2018; El-Manawaty and L. Gohar 2018), while the fruits and fermented fruits of *Morinda citrifolia* have been studied for their antidiabetic potential (So-Young Lee et al. 2012; Simamora et al. 2019; Lolok et al. 2023). Traditionally, plant extracts were prepared using water. However, contemporary research on antidiabetic medicinal plants employs various solvents such as methanol, ethanol, water, ethyl acetate, and chloroform. These solvents extract compounds based on their polarity, which affects the bioactivities

Table 3 In vitro activity of Australian tropical antidiabetic medicinal plants

Species	Part studied	Compound/extract/fraction	Dose	In vitro (cell lines/enzyme inhibitions)	Mechanism/activity	References
<i>Abutilon indicum</i> (L.) Sweet	Whole plant	Water extract	100 µg/mL and 500 µg/mL	HCT-116 cells, L6 myocytes	↑ GLUT1 promoter, ↓ Insulin resistance via PPARα and PPARγ activation	Krisanapun et al. (2011)
	Leaves	Methanol extract	200–800 µg/mL	3T3L1 cells	↑ Glucose uptake/consumption	Lavanya (2022)
		Methanol extract		RIN5F cell lines	↑ Insulin release	Lavanya (2022)
<i>Acacia auriculiformis</i> A.Cunn. ex Benth.	Leaves	Methanolic extract	2–20 µg/mL	Enzyme inhibitions	- Inhibited α-glucosidase (94.259%) and α-amylase (95.259%)	Rangra et al. (2021)
	Stem bark	<i>p</i> -Propoxybenzoic acid	20 µg/mL	Enzyme inhibitions	- Inhibited α-amylase (IC ₅₀ = 50 ± 0.45 µg/mL)	Johnson et al. (2022)
	Leaves	α-Spinasterol	5–100 µg/mL	Enzyme inhibitions	- Inhibited α-glucosidase (IC ₅₀ = 8.65 ± 1.71 µg/mL)	Lawal et al. (2020)
<i>Acacia kempeana</i> F.Muell.	Leaves	Ethanol extract	100 µg/mL	3T3L1 cells	↑ Glucose uptake/consumption	Gulati et al. (2015)
<i>Acalypha wilkesiana</i> Müll.Arg.	Leaves	Ethanol extract	50–250 µg/mL	Enzyme inhibitions	- Inhibited α-glucosidase (EC ₅₀ = 67.18 ± 7.65 µg/mL) and α-amylase (EC ₅₀ = 75.35 ± 8.25 µg/mL)	Oyebo et al. (2018)
		Methanolic extract		Enzyme inhibitions	- Inhibited α-glucosidase (IC ₅₀ = 5.43 ± 0.9 ppm)	May Aly El-Manawaty and Lamiaa Gohar (2018)
	Root bark	Ethanol extract	50–250 µg/mL	Enzyme inhibitions	- Inhibited α-glucosidase (EC ₅₀ = 35.75 ± 1.95 µg/mL) & α-amylase (EC ₅₀ = 6.25 ± 1.05 µg/mL)	Oyebo et al. (2018)
<i>Brucea javanica</i> (L.) Merr.	Seeds	Ethyl acetate fraction	25–500 µg/mL	Enzyme inhibitions	- Inhibited α-glucosidase (IC ₅₀ = 483.93 µg/mL)	Ablat et al. (2017)
		Luteolin	25–500 µg/mL	Enzyme inhibitions	- Inhibited α-glucosidase (IC ₅₀ = 26.41 ± 0.04 µM) and GPα ((IC ₅₀ = 45.08 ± 0.04 µM)	Abdulwali Ablat et al. (2017)
<i>Castanospermum australe</i> A.Cunn. & C. Fraser	Seeds	70% Ethanol extract	2.5–80 µg/mL	Enzyme inhibitions	- Inhibited DPP-IV (IC ₅₀ = 13.96 µg/mL)	Bharti et al. (2012)
		7-Deoxy-6-epi-castanospermine	1 mM	Enzyme inhibitions	- Inhibited yeast α-glucosidase (50%), glucosidase I (35%), intestinal sucrase (30%) and β-galactosidase (20%)	Molyneux et al. (1990a)
		Australine	5.8 µM	Enzyme inhibitions	- Inhibited 50% α-glucosidase and amyloglucosidase	Tropea et al. (1989)

Table 3 continued

Species	Part studied	Compound/extract/fraction	Dose	In vitro (cell lines/enzyme inhibitions)	Mechanism/activity	References
<i>Cleome viscosa</i> L.	Whole plant	FD fraction	20–100 µg/mL	Enzyme inhibitions	- Inhibited α -amylase ($IC_{50} = 25.93 \pm 0.83$ µg/mL) and α -glucosidase ($IC_{50} = 48.76 \pm 0.96$ µg/mL)	Suresh et al. (2020)
<i>Dodonaea viscosa</i> Jacq.	Aerial part, leaves, stem, root	Crude extracts from 14 different solvents	4 mg/10 µL DMSO	Enzyme inhibition	- Moderately inhibited α -amylase	Malik et al. (2022)
<i>Eleocharis dulcis</i> (Burm.f.) Trin. ex Hensch.	Chestnuts	Ethanol extract	2000 ppm	Enzyme inhibition	- Inhibited α -glucosidase (65.74%)	Baehaki et al. (2021)
<i>Ficus racemosa</i> L.	Stem bark	Aqueous extract	1–5 mg/mL	Yeast cells	↑Glucose uptake/consumption	Ahmed and Urooj (2010)
<i>Grewia hirsuta</i> Vahl	Leaves	Chloroform/methanol fraction	100 µg/mL	Enzyme inhibition	- Inhibited α -amylase (52.73%)	Abirami and Natarajan (2014)
	Leaves	(4Z, 12Z)-cyclopentadeca-4, 12-dienone	NA	3T3-L6 cells	- Inhibited α -amylase and α -glucosidase	Natarajan et al. (2015)
<i>Macaranga tanarius</i> Müll.Arg.	Leaves	Macatannin A	NA	Enzyme inhibitions	- Inhibited α -glucosidase ($IC_{50} = 0.80$ mM)	Gunawan-Puteri and Kawabata (2010)
		Macatannin B	NA	Enzyme inhibitions	- Inhibited α -glucosidase ($IC_{50} = 0.55$ mM)	Gunawan-Puteri and Kawabata (2010)
		Chebularic acid	NA	Enzyme inhibitions	- Inhibited α -glucosidase ($IC_{50} = 1.0$ mM)	Gunawan-Puteri and Kawabata (2010)
		Corilagin	NA	Enzyme inhibitions	- Inhibited α -glucosidase ($IC_{50} = 2.63$ mM)	Gunawan-Puteri and Kawabata (2010)
		Malloitic acid	NA	Enzyme inhibitions	- Inhibited α -glucosidase ($IC_{50} > 5.0$ mM)	Gunawan-Puteri and Kawabata (2010)
	Fruits	Isonymphaeol B & 3'-geranyl naringenin	30 µM	L6 rat myoblasts	↑Glucose uptake, ↑AMPK phosphorylation, ↑Glut1 mRNA expression, ↑Plasma membrane GLUT1 protein level	Natsume et al. (2021)
<i>Merremia tridentata</i> (L.) Hallier f.	Stem	50% Ethanol extract	1 mg/mL	Enzyme inhibitions	- Inhibited α -amylase ($IC_{50} = 1.61$ – 1.72 mg/mL) and α -glucosidase ($IC_{50} = 0.24$ – 0.44 mg/mL)	Vo Van et al. (2022)
		Flavonoid-rich fraction	0.1 mg/mL	Enzyme inhibitions		

Table 3 continued

Species	Part studied	Compound/extract/fraction	Dose	In vitro (cell lines/enzyme inhibitions)	Mechanism/activity	References
<i>Morinda citrifolia</i> L.	Fruits	Fermented fruit juice	23.86 µg GAE/mL	Enzyme inhibitions	- Inhibited α -glucosidase (IC ₅₀ = 28.99 ± 4.31 µg/mL)	Simamora et al. (2019)
		Ethanol extract	150, 75, 37.5, 18.75, and 9.375 ppm	Enzyme inhibitions	- Inhibited α -amylase (IC ₅₀ = 14.16 ± 5.72 ppm)	Lolok et al. (2023)
		Stigmastrol	150, 75, 37.5, 18.75, and 9.375 ppm	Enzyme inhibitions	- Inhibited α -amylase (IC ₅₀ = 10.29 ± 0.76 ppm)	Lolok et al. (2023)
	Whole plant	Lirioresinol B, episesamin 2,6-dicatechol	20 µM	3T3-L1 adipocyte cells	↑2-NBDG uptake	Nguyen et al. (2013)
<i>Ocimum gratissimum</i> L.		Lirioresinol B dimethyl ether, Ursolic acid	40 µM			
	Fruits	Fermented <i>M. citrifolia</i> 70% ethanolic extract (FMCE)	50–400 µg/mL	C2C12 cells	↑Glucose uptake via activated-AMPK & PPAR- γ	So-Young Lee et al. (2012)
	Leaves	Pap water extract	0.1–2.5 mg/mL	Enzyme inhibitions	- Inhibition of α -amylase (IC ₅₀ = 0.47 mg/mL) and α -glucosidase (IC ₅₀ = 9.09 µg/mL)	Agunbiade et al. (2024)
	Fruits	(Z)-4H-hydroxy-3-(4-hydroxy-3-methylbut-2-en-1-yl) benzaldehyde	NA	Enzyme inhibitions	- Inhibited α -glucosidase (IC ₅₀ = 192.4 ± 0.2 µM)	Mai et al. (2015)
<i>Pandanus tectorius</i> Parkinson		<i>p</i> -Hydroxybenzaldehyde	NA	Enzyme inhibitions	- Inhibited α -glucosidase (IC ₅₀ = 133.1 ± 0.1 µM)	
		Syringaldehyde	NA	Enzyme inhibitions	- Inhibited α -glucosidase (IC ₅₀ = 125.3 ± 0.3 µM)	
		(E)-Ferulaldehyde	NA	Enzyme inhibitions	- Inhibited α -glucosidase (IC ₅₀ = 36.5 ± 0.1 µM)	
		(E)-Sinapinaldehyde	NA	Enzyme inhibitions	- Inhibited α -glucosidase (IC ₅₀ = 69.5 ± 0.4 µM)	
		Vanillin	NA	Enzyme inhibitions	- Inhibited α -glucosidase (IC ₅₀ = 81.5 ± 0.2 µM)	

Table 3 continued

Species	Part studied	Compound/extract/fraction	Dose	In vitro (cell lines/enzyme inhibitions)	Mechanism/activity	References
<i>Syzygium cumini</i> (L.) Skeels	Leaves	Aqueous extract	10–100 µg/mL	Enzyme inhibitions	- Inhibited α -amylase (IC_{50} = 8.3 µg/mL) and α -glucosidase (IC_{50} = 6.64 µg/mL)	Mahindrakar and Rathod (2022)
	Bark	Chloroform fraction	0.2 µg/mL	Enzyme inhibitions	- Inhibited α -glucosidase (IC_{50} = 77.09 ± 1.98 µM)	Mujawah et al. (2023)
		Friedelin	0.2 µg/mL	Enzyme inhibitions	- Inhibited α -glucosidase (IC_{50} = 17.54 ± 1.54 µM)	
	Fruits	Methanol extracts of kernel, seeds, seed coat, & pulp	0.1–300 µg/mL	Enzyme inhibitions	- Inhibited α -amylase (IC_{50} = 8.3, 12.9, 50.8, 270 µg/mL, respectively)	Gajera et al. (2017b)
	Seeds	Ethyl acetate fraction	Up to 100 µg/mL	Enzyme inhibitions	- Inhibited PTP1B (IC_{50} = 26.36 µg/mL) and AR (IC_{50} = 2.50 µg/mL)	Sawant et al. (2015)
		Gallic acid		Enzyme inhibitions	- Inhibited AR (IC_{50} = 0.77 µg/mL)	
		Valoneic acid dilactone		Enzyme inhibitions	- Inhibited AR (IC_{50} = 0.075 µg/mL)	
<i>Terminalia catappa</i> L.		Rubuphenol			- Inhibited AR (IC_{50} = 0.165 µg/mL)	
		Ellagic acid			- Inhibited AR (IC_{50} = 0.12 µg/mL)	
		70% Methanol fraction	0–60 µg/mL	Enzyme inhibitions	- Inhibited α -glucosidase (IC_{50} = 1.7 mg/mL) and α -amylase (IC_{50} = 7.62 mg/mL)	Syama et al. (2018)
		Methanol fraction	10 µg/mL		- Inhibited DPP-IV (88.1%)	
		70% Methanol fraction	10 µg/mL	L6 myocytes	↑2-NBDG uptake (26.9%)	
	Fruits	Methanol extract	31.25, 62.5, 125, 250, 500, 1000 µg/mL	Enzyme inhibitions	- Inhibited α -glucosidase (IC_{50} = 1.04 ± 0.02 mg/mL) and α -amylase (IC_{50} = 0.19 ± 0.06 mg/mL)	Amelia et al. (2024)
		Ethyl acetate extract		Enzyme inhibitions	- Inhibited α -glucosidase (IC_{50} = 3.20 ± 1.72 mg/mL) and α -amylase (IC_{50} = 0.20 ± 0.03 mg/mL)	

AMPK 5' AMP-activated protein kinase, AR aldose reductase, DPP-IV dipeptidyl peptidase-IV, EC_{50} half-maximal effective concentration, IC_{50} half-maximal inhibitory concentration, GLUT1 glucose transporter 1, GP α the P4 specific replication protein, PPAR α peroxisome proliferator-activated receptor- α , PPAR γ peroxisome proliferator-activated receptor- γ , PTP1B protein tyrosine phosphatase 1B, 2-NBDG 2-[N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl) amino]-2-deoxy-D-glucose

of the extracts. For instance, *Terminalia catappa* fruit extracted using methanol and ethyl acetate exhibited different antidiabetic activities in vitro, with the methanol extract showing higher activity (Fitri Amelia et al. 2024). Similar results were observed with *Acalypha wilkesiana* leaves extracted using methanol and ethanol, where the methanol extract demonstrated better activities (Oyeboode et al. 2018; El-Manawaty and L. Gohar 2018).

The mechanism of action of plant crude extracts was also studied by using various cell lines (Table 3, Fig. 6). These assays target receptors involved in insulin signalling pathways. For example, the aqueous extract of *Abutilon indicum* increased glucose utilisation via glucose transporter-1 (GLUT1) (Chutwadee Krisanapun et al. 2011). Fermented fruit extract of *Morinda citrifolia* enhanced glucose uptake by activating adenosine 5'-monophosphate-activated protein kinase (AMPK) (So-Young Lee et al. 2012). Methanol and water extracts of *Orthosiphon aristatus* aerial parts scavenged the oxidants and boosted the translocation of glucose transporter-4 (GLUT4) to the plasma

membrane in skeletal muscles (Bassalat et al. 2023), while fruit extract from *Pandanus tectorius* reduced insulin resistance by activating the AMPK–AS160–GLUT4 pathway in skeletal muscles and suppressing gluconeogenesis and lipogenesis in the liver (Fig. 6) (Wu et al. 2014).

Most in vivo antidiabetic studies of plant crude extracts were conducted in T2D rodent models. Chemically-induced diabetic rodent models using streptozotocin (STZ) or alloxan chemicals with glibenclamide or metformin as standard drugs were the most common in in vivo studies (Table 4). From in vivo studies, crude extracts lowered blood-glucose levels, reduced hemoglobin A1c (HbA1c) levels, and improved insulin sensitivity. For example, *C. australe* seed extract (100 and 150 mg/kg bw) significantly reduced the elevated blood glucose levels and improved Haemoglobin A1c (HbA1c) and insulin levels in T2D rats ($p \leq 0.001$) (Sudhanshu Kumar Bharti et al. 2012). Similarly, ethanol extract from leaves and flowers of *Melastoma affine* (150 and 300 mg/kg bw) lowered blood glucose levels and

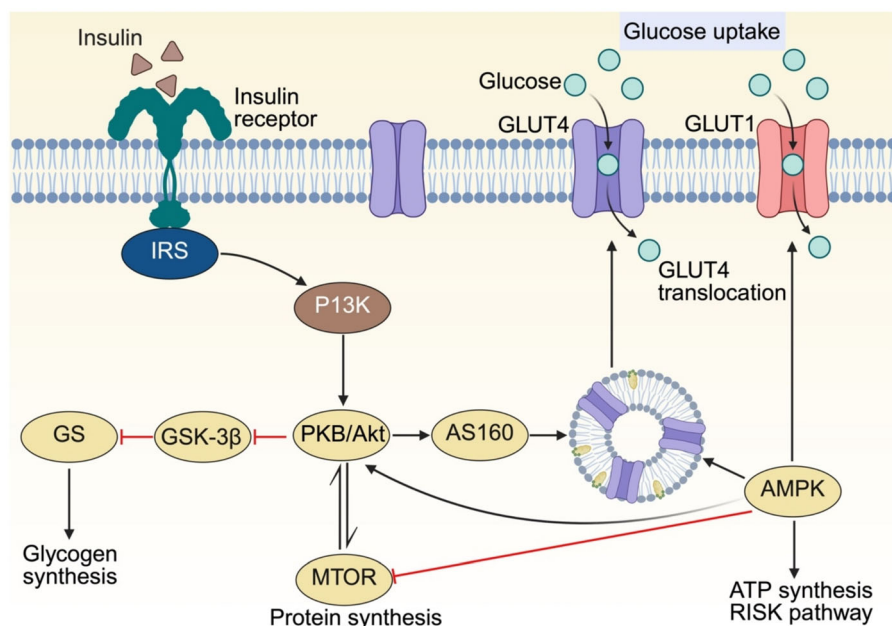


Fig. 6 Targeted molecular modes of crude extracts and isolated compounds in the insulin signalling pathway (Litwiniuk et al. 2021; Izundegui and Naylor 2022). Insulin works by interacting with specific receptors on target cells, known as insulin receptors (IRs), which include insulin receptor substrate (IRS). When insulin binds to these receptors, it activates an enzyme called phosphatidylinositol 3-kinase (PI3K), which triggers a

series of reactions leading to the activation of another enzyme, protein kinase B (PKB or AKT). AKT then modifies a protein called glycogen synthase kinase-3 beta (GSK-3β) by adding a phosphate group at the Ser9 site, which reduces its activity. This PI3K/AKT/GSK-3β signalling pathway plays a critical role in insulin signalling and is crucial for regulating glycogen synthesis (Litwiniuk et al. 2021; Izundegui and Naylor 2022)

Table 4 In vivo activity of Australian Tropical antidiabetic medicinal plants

Species	Part studied	Compound/ extract/fraction	Dose	In vivo model	Activity/mechanism of action	References
<i>Abutilon indicum</i> (L.) Sweet	Leaves	Methanol extract	500 mg/kg bw	Wistar rats (STZ- induced)	↓Plasma glucose level, ↓ ∞ -glucosidase	Adisakwattana et al. (2009)
		Ethanol extract	400 mg/kg bw	Wistar rats (normal)	↓Blood glucose level, ↑GLUT1 activity, ↑PPAR γ activation	Seetharam et al. (2002)
	Whole plant	Aqueous extract	0.25 & 0.5 g/kg bw	Wistar rats (STZ- induced)	↓Postprandial plasma glucose level	Krisanapun et al. (2011)
		Aqueous extract	0.5 & 1 g/ kg bw	Wistar rats, Swiss Albino mice (STZ-induced)	↓Plasma glucose level	Krisanapun et al. (2009)
<i>Acacia auriculiformis</i> A.Cunn. ex Benth.	Bark	70% Acetone extract	200 & 400 mg/ kg bw	Sprague-Dawley (SD) albino rats (alloxan monohydrate- induced)	↓Blood glucose level	Sathya and Siddhuraju (2013)
	Empty pod		100 & 200 mg/ kg bw			
<i>Acalypha wilkesiana</i> Müll.Arg.	Roots	Methanol extract	200 & 400 mg/ kg bw	Wistar rats (alloxan monohydrate- induced)	↓FBG level, ↓Serum TC, ↓Serum TG, ↓SGOT, ↓SGPT	Odoh et al. (2014)
	Leaves	Aqueous extract	500 mg/kg bw	Rats (alloxan- induced)	↓FBG level	Agunbiade et al. (2012)
<i>Ageratum conyzoides</i> L.	Leaves, stems, and roots	Methanol extract	100 mg/kg bw	Wistar rats (STZ- induced)	↓FBG level, ↓TC, ↓LDL	Atawodi et al. (2017)
	Leaves and fruits	Aqueous extract	30 mg/kg bw	Rats (STZ-induced)	↑Serum insulin, ↓Serum glucose level	Kamaei and Moghadamnia (2021)
	Leaves	80% Ethanol extract	100 mg/kg bw, 200 mg/ kg bw	Wistar rats (alloxan monohydrate- induced)	↓Bax, ↓Bcl-2, ↓Caspase-9, ↓MDA, ↓HOdG-8, ↓Serum TNF, IL-1 β , & IL-6	Sadoughi and Hosseini (2020)
<i>Avicennia marina</i> (Forssk.) Vierh.	Seeds	Ethyl acetate fraction	25 & 50 mg/kg bw	SD rats (STZ- induced)	↓Blood glucose level, ↑Insulin, ↑Glycogen, ↓Oxidative stress & inflammation, ↓Lipids level	Abdulwali Ablat et al. (2017)
<i>Brucea javanica</i> (L.) Merr.		96% Ethanol extract	30 mg/kg bw	Wistar rats (Alloxan-induced)	↓FBG level, ↑Insulin secretion, ↑Body weight, β -cells in Islets of Langerhans	Muliasari et al. (2019)

Table 4 continued

Species	Part studied	Compound/ extract/fraction	Dose	In vivo model	Activity/mechanism of action	References
<i>Cassytha filiformis</i> L.	Whole plant	Water, ethyl acetate (EtOAc) and butanol (BuOH) fractions	10 mg/kg bw	Mice (Alloxan-induced)	↓Blood glucose level	Armenia et al. (2016)
	Aerial parts	80% Methanol extract fractions	600 mg/kg bw	Albion mice (Alloxan monohydrate-induced)	↓FBG level, ↓Serum MDA, ↓TC	Nwaehujor et al. (2021)
<i>Castanospermum australe</i> A.Cunn. & C.Fraser	Seeds	70% Ethanol extract	100 & 150 mg/kg bw	Wistar rats (Poloxamer-407-induced)	↓Blood glucose level, ↓HbA1c, ↓Insulin, ↓HOMA-R	Sudhanshu Kumar Bharti et al. (2012)
<i>Cleome viscosa</i> L.	Whole plant	Ethanol extract	100, 200, & 400 mg/kg bw	Wistar rats (STZ-induced)	↓LPO, ↓Lipids, ↓Oxidative stress	Rao et al. (2014)
<i>Clerodendrum inerme</i> Gaertn.	Leaves	45% Ethanol extract	343 & 686 mg/kg bw	Swiss Albino mice	↓Plasma glucose level, ↓MDA in liver & kidney, ↓Oxidation stress, ↑Pancreatic β-cells	Ly et al. (2019)
		Ethanol extract	400 mg/kg bw	Wistar rats (STZ-induced)	↓Blood glucose level	Bharat Bhushan et al. (2015)
<i>Dodonaea viscosa</i> Jacq.	Leaves	Hydromethanolic extract	500 mg/kg bw	Rabbits (Alloxan monohydrate-induced)	↓Body weight, ↓Blood glucose level	Akhtar et al. (2011)
		Methanol extract	150 & 300 mg/kg bw	Albino Wistar rats (STZ-induced)	↓Blood glucose level, ↓Proinflammatory cytokines, ↑Insulin level	Jangra et al. (2011)
	Aerial parts	Aqueous extract	400 mg/kg bw	Wistar rats	↓Blood glucose level	Veerapur et al. (2010)
		Polar fraction of ethanol extract	200 mg/kg bw		↓Blood glucose level	
		Viscosol	33 mg/kg bw	C57BL/6 mice (HFD, STZ-induced)	↓FBG level, ↑Body weight, ↑Liver profile, ↓Oxidative stress, ↓PTP1B expression	Sohail et al. (2022)

Table 4 continued

Species	Part studied	Compound/ extract/fraction	Dose	In vivo model	Activity/mechanism of action	References
<i>Ficus racemosa</i> L.	Stem bark	Methanol extract	200 and 400 mg/ kg bw	Wistar Albino rats (alloxan-induced)	↓Blood glucose level	Bhaskara Rao et al. (2002)
		Ethanol extract	200 and 400 mg/ kg bw	Wistar Albino rats (STZ-induced)	↓Blood glucose level, ↓Lipid level, ↓Creatine kinase, ↓LDH, ↓CRP, ↓Creatinine, ↓Blood urea nitrogen, ↓MDA, ↓Collagen, ↓Albumin	Joshi et al. (2016)
		95% Ethanol extract	300 mg/kg bw	Wistar Albino rats (alloxan monohydrate- induced)	↓Blood glucose level, ↓Lipids, ↓Lipoproteins	Sophia and Manoharan (2007)
	Fruits	α-Amyrin acetate	100 mg/kg bw	Albino rats (STZ- induced)	↓Blood glucose level	Narendar et al. (2009)
	Leaves	β-Sitosterol, lanosterol	100 mg/kg bw	Wistar Albino rats (STZ-induced)	↓Blood glucose level, ↓Serum lipids, ↓HDL, ↓Oxidative stress	Kushwaha et al. (2015)
<i>Flagellaria indica</i> L.	Aerial part	Ethanol extract	250 & 500 mg/ kg bw	Swiss Albino mice	↓Blood glucose level	Karmakar et al. (2021)
<i>Heliotropium indicum</i> L.	Whole plant	Methanol fraction	750 mg/kg bw	Wistar Albino rats (STZ-induced)	↓Blood glucose level	Mohammad et al. (2014)
<i>Hibiscus vitifolius</i> L.	Flowers	Gossypin	20 mg/kg bw	Wistar Albino rats (STZ-induced)	↓Blood glucose level, ↑Plasma insulin, ↓HbA1c, ↑Glycogen content, ↓Plasma proteins, ↓Blood urea	Venkatesan and Sorimuthu Pillai (2012)
<i>Hydrolea zeylanica</i> (L.) Vahl.	Leaves	Hydroalcoholic extract fraction	400 mg/kg bw	Wistar Albino rats (STZ-induced)	↑Glucose homeostasis, ↓Insulin resistance, ↓Inflammatory markers, ↑GLUT2 & GLUT4 expression	Swain et al. (2024)
<i>Macaranga tanarius</i> Müll.Arg	Leaves	Hydromethanolic fraction	50 & 100 mg/ kg bw	db/db mice (C57BLKS/J Iar- + Lep rd /b/ + Lep rd /b)	↓Nephropathy, ↓Fibronectin & collagen IV expression	Hsu et al. (2023)
<i>Melastoma affine</i> D.Don	Leaves, flower	Ethanol extract	150 & 300 mg/ kg bw	Wistar Albino rats (alloxan monohydrate- induced)	↑Body weight, ↓Blood glucose level, ↓HbA1c	Balamurugan et al. (2014)

Table 4 continued

Species	Part studied	Compound/ extract/fraction	Dose	In vivo model	Activity/mechanism of action	References
<i>Merremia tridentata</i> (L.) Hallier f.	Roots	Aqueous extract	50 mg/kg bw	Wistar Albino rats (STZ-induced)	↓Blood glucose level, ↑Body weight, ↑Serum insulin, ↓TC, ↓Glycogen content, ↓Serum TG, ↓LPO	Arunachalam and Parimelazhagan (2012)
	Stem	Ethanol extract	100 mg/kg bw	Swiss Albino mice (alloxan-induced)	↓Blood glucose level, ↑Body weight	Vo Van et al. (2022)
<i>Morinda citrifolia</i> L.	Fruits	Ethanol extract	300 mg/kg bw	Wistar Albino rats (STZ-induced)	↓Blood glucose level, ↓HbA1c, ↓Blood urea, ↓Serum creatinine, ↓Plasma insulin, ↓Plasma hemoglobin	Mahadeva Rao and Subramanian (2009)
	<i>M. citrifolia</i> fermented by Cheonggukjang (FMC) Leaves	70% Ethanol extract	Fed AIN-93G with 0.4% FMC	KK-Ay/TaJcl mice (banana-fed)	↓HbA1c level, ↑Insulin sensitivity, ↓LDL-c, ↓Serum TG	Lee et al. (2012)
<i>Ocimum gratissimum</i> L.	Leaves	Aqueous extract	400 mg/kg bw	Wistar rats (Dexamethasone-induced)	↓Body weight, ↓FBG level, ↓Insulin, ↓HOMA-IR	Shittu et al. (2021)
	Leaves	Chicoric acid	3 mg/kg bw	Swiss mice (STZ-induced)	↓Blood glucose level	Casanova et al. (2014)
		Leaf decoction	10% p/v	Swiss mice (STZ-induced)	↓Blood glucose level	Casanova et al. (2014)
		Aqueous extract	500 mg/kg bw	Wistar rats (STZ-induced)	↓Blood glucose level	A et al. (2007)
<i>Ocimum tenuiflorum</i> L.	Leaves	Methanol extract	1 g/kg bw	SD rats (STZ-induced)	↓FBG level	Mousavi et al. (2016)
		60% Ethanol extract	250 & 500 mg/kg bw	Wistar Albino rats (STZ-induced)	↓Body weight, ↓Blood glucose level, ↓Serum TC, ↓TG, ↓LDL-c, ↓VLDL-c	Parasuraman et al. (2015)
<i>Pandanus tectorius</i> Parkinson	Fruit	70% Ethanol fraction	50–200 mg/kg bw	C57BL/6 (HFD)	↓Body weight, ↓FBG level, ↓Insulin, ↑GLUT4 expression & translocation, ↓Glucose & gluconeogenic precursors, ↓Gluconeogenic enzyme G6Pase & PEPCK expressions	Wu et al. (2014)

Table 4 continued

Species	Part studied	Compound/ extract/fraction	Dose	In vivo model	Activity/mechanism of action	References
<i>Syzygium cumini</i> (L.) Skeels	Fruits	Methanol extract	200 mg/kg bw	C57BL/6 (HFD)	↓Blood glucose level, ↑Insulin sensitivity, ↑Glucose tolerance, ↓Hepatic injury, ↓Nephrotoxicity, ↓Lipid markers (TC, TG, LDL-c, VLDL-c levels), ↓Body weight, ↓Adiposity	Thiyagarajan et al. (2024)
	Seeds	Hydroethanolic extract	75 mg/kg bw	Wistar Albino rats (alloxan monohydrate-induced)	↓Blood glucose level, ↑Body weight	Gopal Thiyagarajan et al. (2024)
		96% Ethanol extract	10% in a 1% CMC-Na suspension	Wistar rats (alloxan-induced)	↓Blood glucose level	Dira (2022)
<i>Terminalia catappa</i> L.		Cuminoside	50 mg/kg bw	Wistar Albino rats (Tween 80-induced)	↓FBG level, ↓LDL, TC, TG, ↑Hepatic enzymes (AST, ALT, LDH) levels	Farswana et al. (2009)
		Mycaminose	50 mg/kg bw	Wistar rats (STZ-induced)	↓Blood glucose level	Kumar et al. (2008)
	Fruits	Aqueous extract	42 mg/kg bw	Wistar Albino rats (alloxan-induced)	↓Blood glucose level, ↓Body weight, ↓Serum cholesterol, TG, LDL-c, HDL-c	Nagappa et al. (2003)
		Petroleum ether extract	68 mg/kg bw			
		Methanol extract	40 mg/kg bw			
	Leaves	Ethanol extract	50 mg/kg bw	BALB/c mice (STZ-induced)	↑Body weight, ↑Tissue glucose tolerance, ↑Langerhans islet diameter, ↓FBG level	Hayaza et al. (2019)
<i>Ziziphus oenoplia</i> (L.) Mill.		Aqueous extract	400 & 800 mg/kg bw	Wistar rats (HFD)	↑Insulin resistance, ↑Glucose transport, ↑PI3K/AKT signalling	Iheagwam et al. (2022)
	Fruits	Ethanol extract	100, 200, & 400 mg/kg bw	Rats (STZ-induced)	↓Blood glucose level, ↓TC, ↓TG, ↓LDL	Goyal and Jeyabalan (2021)

Table 5 Clinical studies of Australian tropical antidiabetic medicinal plants

Species	Part studied	Extract/fraction	Dose	Treatment frequency	In vivo model	Activity/mechanism of action	References
<i>Eleocharis dulcis</i> (Burm.f.) Trin. ex Hensch.	Fruits	Fruits powder mixed with <i>Brassica rapa</i> roots powder	500 g with salad (orally)	Once per day for 3 weeks	T2D patients	↓Blood glucose level	Arif et al. (2022)
<i>Morinda citrifolia</i> L.	Fruits	Juice	2 ml/kg bw	Once per day for 8 weeks	T2D patients	↓FBG level, ↓HbA1c level, ↓hs-CRP	Algenstaedt et al. (2018)

hs-CRP high sensitivity C-reactive protein, HbA1c Hemoglobin A1c, T2D type 2 diabetes

HbA1c in alloxan-induced diabetic rats (Balamurugan et al. 2014). *Syzygium cumini* seed extract demonstrated significant antidiabetic effects by reducing blood glucose levels in both chemically-induced and high-fat diet (HFD)-induced rodent models of experimental T2D at various dosages of body weight (bw) (Gopal Thiagarajan et al. 2024). Moreover, some crude extracts from medicinal plants were further clinically tested in diabetic patients (Table 5). For example, fruit extract of *Eleocharis dulcis* (mixed with *Brassica rapa* root) and *Morinda citrifolia*, has been tested in T2D patients and showed blood glucose levels reduction (Arif et al. 2022; Algenstaedt et al. 2018) (Table 5).

In vivo testing in diabetic animal models have also evaluated the effectiveness of crude extracts in mitigating T2D-related complications, including cardiovascular diseases, diabetic retinopathy, and liver and kidney injuries (Table 4). Studies have shown that ethanol extract of *Ocimum tenuiflorum* leaves (250 and 500 mg/kg bw) and *Ziziphus oenoplia* fruits (100, 200, and 400 mg/kg bw) reduced lipid profile parameters, such as total triglycerides, total cholesterol, low-density lipid cholesterol (LDL-c) and high-density lipid cholesterol (HDL-c) (Parasuraman et al. 2015; Goyal and Jeyabalan 2021). These parameters are crucial for assessing hypercholesterolemia, a condition linked to increased cardiovascular disease risk in T2D patients (Khil et al. 2023). Additionally, a study observed cardiovascular risk reduction in diabetic rats treated with *Ficus racemosa* stem bark ethanol extract (200 and 400 mg/kg bw), which decreased the expression of marker proteins creatine kinase and creatinine (Joshi et al. 2016). For diabetic retinopathy, the expression of apoptotic factors Bax and Bcl-2, a marker of the condition (Khalfaoui et al. 2010), was

reduced by *Avicennia marina* ethanol leaves extract (100 and 200 mg/kg bw) (Sadoughi and Hosseini 2020). Some plant crude extracts also reduced the risk of liver and kidney injuries. For instance, methanol extract of *Acalypha wilkiseana* root decreased levels of serum glutamate pyruvate transaminase (SGOT) and serum glutamate pyruvate transaminase (SGPT), key enzymes linked to liver health (Odoh et al. 2014), and *Syzygium cumini* fruit extract lowered nephrotoxicity (hepatic injury) (G. Thiagarajan et al. 2024). *Macaranga tanarius* leaves extract, and *Morinda citrifolia* fruit extract reduced the risk of kidney injury (nephropathy) by lowering some markers, including fibronectin and collagen IV expressions and serum creatine levels (Hsu et al. 2023; Mahadeva Rao and Subramanian 2009). Furthermore, the extract of *S. cumini* and *Avicennia marina* showed recovery from histological hepatic and kidney injury (Sadoughi and Hosseini 2020, G. Thiagarajan et al. 2024).

2. Antidiabetic phytochemicals

A total of 374 compounds from 26 Australian tropical medicinal plant species have been isolated and characterised thus far (Table 6). Of the total 374 compounds, 51 compounds from 17 medicinal plant species have undergone in vitro and/or in vivo testing to confirm their antidiabetic properties and ethnopharmacological applications (Tables 3 & 4). A total of 16 compounds were identified as promising antidiabetic drug leads (Fig. 7). The most tested compounds were isolated from *Brucea javanica*, *Syzygium cumini*, *Macaranga tanarius*, and *Pandanus tectorius*. Luteolin (1) (isolated from *Brucea javanica*) was the most potent inhibitor of glycoprotein- α (GP- α) and α -glucosidase. Its GP- α inhibitory activity (IC₅₀ = 45.08 μ M) was 10 times greater than that of the

Table 6 Isolated compounds from Australian tropical medicinal plants

Species	Part studied	Isolated compounds	References
<i>Abutilon indicum</i> (L.) Sweet	Leaves, whole plant	Methyl <i>trans</i> - <i>p</i> -coumarate; methyl caffeate; syringic acid; pinellac acid; abutilin; (R)-N-(1'-methoxycarbonyl-2'-phenylethyl)-4'-hydroxybenzamide; syringaldehyde; alantolactone; isolantalactone	Khan et al. (2015), Kuo et al. (2008), Musthafa et al. (2021), Sharma and Ahmad (1989)
<i>Acacia auriculiformis</i> A.Cunn. ex Benth.	Heartwood, stem bark, funicles, leaves	(2S,3R,4R)-2-(3-Hydroxyphenyl)-4-methoxychromane-4,7,8-triol; (E)-3-(4-hydroxyphenyl)-1-(2,3,4-trihydroxyphenyl)prop-2-en-1-one; <i>trans</i> -2,3'-3,4',7,8-tetrahydroxyflavanone; 3,4',7,8-tetrahydroxyflavone; teracadin; (2R,3R,4R)-2-(3-hydroxyphenyl)-4-methoxychromane-4,7,8-triol; acaciaside A & B; α -spinasterol; botulin; <i>p</i> -propoxybenzoic acid	Lawal et al. (2020), Ahmadu et al. (2021), Prayogo et al. (2023), Mandal et al. (2005), Johnson et al. (2021)
<i>Acalypha wilkesiana</i> Müll.Arg.	Leaves; root and root bark	Gallic acid; corilagin; geraniin; rutin; kaempferol 3- <i>O</i> -rutinoside	Adesina et al. (2000)
<i>Ageratum conyzoides</i> L.	Leaves, stem, root, Whole plant	5,6,7,8,3,4,5-Heptamethoxyflavone; 5,6,7,8,3-pentamethoxy-4,5-methylenedioxyflavone; coumarin; ageconylflavones A (5,6,7-trimethoxy-3',4'-methylenedioxyflavone); ageconylflavones B (5,6,7,3'-tetramethoxy-4'-hydroxyflavone); ageconylflavones C (5,6,7,3',5'-pentamethoxy-4'-hydroxyflavone); linderoflavone B; eupalestin; nobiletin; 5'-methoxynobiletin, 5,6,7,5'-tetramethoxy-3',4'-methylenedioxyflavone; sinensetin; 5,6,7,8,3'-pentamethoxy-4'-hydroxyflavone and 5,6,7,8,3',5'-hexamethoxy-4'-hydroxyflavone; 5,6,7,3',4',5'-hexamethoxyflavone; 5,6,7,8,3',4'-hexamethoxyflavone (nobiletin); 3',4'-methylenedioxy-5',5,6,7-tetramethoxyflavone; 5,6,7,8,5'-pentamethoxy-3',4'-methylenedioxyflavone	Moreira et al. (2007), Vyas and Mulchandani (1986), Binh et al. (2021)
<i>Avicennia marina</i> (Forssk.) Vierh.	Leaves and fruits, aerial	1,3-Benzodioxole, 5,5'-(tetrahydro-1H,3H-Furo[3,4-c]furan-1,4-diyl)bis-, [1 s- (1 α ,3 α ,4 β ,6 α α)] 11-hydroxy-8,11,13-abietatriene 12-O-beta-xylopyranoside; 6H α -11,12,16-trihydroxy-6,7-secoabietatriene-8,11,13-triene-6,7-dial 11,6-hemiacetal; 6H β -11,12,16-trihydroxy-6,7-secoabietatriene-8,11,13-triene-6,7-dial 11,6-hemiacetal; (7'S*,8'R*)-4',9'-trihydroxy-3,3',5,5'-tetramethoxy-7,8-dehydro-9-al-2,7'-cycloglignan; 6,11,12,16-tetrahydroxy-5,8,11,13-abietetraen-7-one; lyoniresinol; lyoniresinol 9'- <i>O</i> -beta-D-glucopyranoside; diacetylmaritinoside (Han et al. 2008); 2'- <i>O</i> -(5-phenyl)-2E, 4E-pentadienyl) musaenosidic acid	Devi et al. (2014), Feng et al. (2006)
<i>Brucea javanica</i> (L.) Merr.	Seed	Brusatol; bruceantin; brucein A; bruceantanol; brucein B; 20-hydroxyadanzigan; yadanzigan; bruceine F; bruceine E; javanicolides C & D; javanicosides B – F; yadanziolide A; bruceine D; javanicolides A & B; vanillic acid; bruceine E; <i>p</i> -hydroxybenzoic acid; luteolin; protocatechuic acid; gallic acid	Ryu et al. (2017), Yanzhi Zhan et al. (2020), Liu et al. (2012), Kim et al. (2004), Fukamiya et al. (1992), Kim et al. (2003), Abdulwali Ablat et al. (2017)

Table 6 continued

Species	Part studied	Isolated compounds	References
<i>Cassytha filiformis</i> L.	Whole plant	Precassuthine; (+)-6S-ocotectine-N-oxide; isofliformine; cassythine acid; cassithine; neolitsine; dicentrine; 1, 1,2-methylenedioxy-3,10,1-trimethoxyaporphine; (-)-O-methylflavinatine; (-)-salutaridine; isohammetin-3-O- β -glucoside; isohammetin-3-O-rutinoside	Huang et al. (2022), Tsai et al. (2008)
<i>Castanospermum australe</i> A.Cunn. & C.Fraser	Leaves, stem, wood	1-Epialexine; 2 β ,23-dihydroxy-3-O-(4-deoxy- β -1-threo-hex-4-enopyranosiduronic acid)-olean-12-en-28-oic acid dimethyl ester; medicagenic acid 3-O- β -D-glucoside dimethyl ester; castanospermine (1,6,7,8-tetrahydroxy-octahydroindolizidine); koparin (7,3',4'-trihydroxy-2'-methoxyisoflavone or 7,2',3'-trihydroxy-4'-methoxyisoflavone); 7-Deoxy-6-epi-castanospermine; berberin; 6-epi-castanospermine; 3-epi-australine (3,7a-di-epi;-alexine); 1-epi-australine	Jones et al. (2010), Uddin Ahmad et al. (1992), Campbell et al. (1987), Berry et al. (1977), Sudhanshu Kumar Bharti et al. (2012), Molyneux et al. (1990b)
<i>Cleome viscosa</i> L.	Whole plant	Cembrenoid diterpene; malabaric acid; stigmast-4-en-3-one; stigmast-4-ene-3,6-dione; allantoin; atropine; nevirapine; gallic acid; caffeic acid; vanillic acid; kaempferitin; lactam nonanoic acid (LNA) [2-amino-9-(4-oxoazetidin-2-yl)-nonanoic acid; cleomiscosins A-C; imperatorin	Dissanayake et al. (2022), Lakshmanan et al. (2019), Sharma and Shrivastav (2022), Jana and Biswas (2011), Meena et al. (2011), Lakshmanan et al. (2024)
<i>Clerodendrum inerme</i> Gaertn.	Leaves, stem, aerial, flower	Inermes A & B; 14,15-dihydro-15 beta-methoxy-3-epicaryoptin; 14,15-dihydro-15-hydroxy-3-epicaryoptin; icartol A; syringaresinol-4-O-beta-glucopyranoside; laticresinol-4-O-beta-D-glucopyranoside; dehydrodiconiferyl alcohol-4-O-beta-D-glucopyranoside; leonuride A; sammiangaosides A, B and C; 3-hydroxy-3',4'-dimethoxychalcone; 3,2'-dihydroxy-3',4'-dimethoxychalcone; 7-O-methylwogonin; eucalyptin; crolerodendrum B; and other compounds as reported in Chan et al. (2023)	Pandey et al. (2005), Minh and Thuong (2021), Kanchanapoom et al. (2001), Shahabuddin et al. (2013), Ba Vinh et al. (2018), Chan et al. (2023)
<i>Dodonaea viscosa</i> Jacq.	Aerial part, leaves	Dodovisnoids A-G; 3,5,7,3',4'-pentahydroxyflavone; hautriwaic acid; clerodane diterpenoids 1 and 2; 13,14-dihydroxy-15,16 dimethoxy-(-)-6a-hydroxy-5a,8a,9a,10a-cleroda-3-en-18-oic acid 1; (-)-6a-hydroxy-5a,8a,9a,10a-cleroda-3,13-dien-16,15-olid-18-oic acid 2, 1-L-O-methyl-2-acetyl-3- <i>p-cis</i> -coumaryl-myoinositol; methyl dodovisate A; methyl dodovisate B; 5,7,4'-trihydroxy-3',5'-di(3-methylbut-2-enyl)-3,6-dimethoxyflavone and 5,7,4'-trihydroxy-3'-(4-hydroxy-3-methylbutyl)-5'-(3-methylbut-2-enyl)-3,6-dimethoxyflavone; dodonic acid; hautriwaic acid; hautriwaic lactone; (+)-hardwickic acid; 5-hydroxy-1,2-dehydro-5,10-dihydroprintzianic acid methyl ester; strictic acid; dodonolide; aliarin; 2,18-dihydroxylabda-7,13(E)-dien-15-oic acid; 5,7-dihydroxy-3,6,4'-trimethoxy-3'-(4-hydroxy-3-methyl-but-2-enyl)flavone	Zhang et al. (2016), Hamed Al Bimani and Hossain (2020), Mostafa et al. (2014), Niu et al. (2010), Wabo et al. (2012)

Table 6 continued

Species	Part studied	Isolated compounds	References
<i>Eleocharis dulcis</i> (Burm.f.) Trin. ex Hensch.	Whole plants, peels	Hexacosanoic acid; 5 alpha-stigmastane-3,6-dione; beta-sitosterol; stigmasterol; betulin; and tricin; orcinol glucoside; leonuriside A; 2-hydroxymethyl-6-(5-hydroxy-2-methyl-phenoxy-methyl)-tetra-hydro-pyran-3,4,5-triol; 1,4-dihydroxy-3-methoxy-phenyl-4-O-beta-D-glucopyranoside; 4',5'-dimethoxy-6,6-dimethylpyranoisoflavone; 3-methoxy-4-hydroxylonchocarpin; 4-hydroxylonchocarpin; 4-methoxylonchocarpin; barbigeron; lonchocarpusone; 6a,12a-dehydrodeguelin; 13-homo-13-oxa-6a, 12a-dehydrodeguelin and deguelin	Miles et al. (1994), Nie et al. (2019), Li et al. (2023)
<i>Ficus racemosa</i> L.	Bark	Lupeol; beta-sitosterol; (rel)-4,6-dihydroxy-5-[3-methyl-(E)-propenoic acid-3-yl]-7-beta-glucopyranosyl-(2alpha,3beta-dihydrobenzofuran)-(3,2:b)-[4alpha,5beta-dihydroxy-6alpha-hydroxymethyltetrahydropyran](racemoseic acid); α -amyrin acetate	Bopage et al. (2018), Li et al. (2004), Narendar et al. (2009)
<i>Grewia hirsuta</i> Vahl.	Leaves	(4Z, 12Z)-Cyclopentadeca-4, 12-dienone	Abirami and Natarajan (2014)
<i>Heliotropium indicum</i> L.	Leaves, root, whole plant	Helindicine; lycopsamine; (E)-ethyl-12- cyclohexyl-4,5-dihydroxydodec-2-enoate	Souza et al. (2005), López-Lorenzo et al. (2022)
<i>Hibiscus vitifolius</i> L.	Root, flower	Vitiquinolone, β -Amyrin acetate; n-octacosanol; β -amyrin; stigmasterol; xanthyletin; alloxanthyletin; xanthoxyletin; betulinic acid; methyl 27-caffeoyloxyoleanolate; oleanolic acid; kaempferol; quercetin; β -sitosterol-3-O- β -D-glucopyranoside; kaempferol-3-O- α -D-rhamnopyranoside; gossypin; quercetin-3-O- β -D-glucopyranoside; mangiferin; gossypin	Ramasamy and Saraswathy (2014), Ramasamy and Saraswathy (2013), Venkatesan and Sorimuthu Pillai (2012)
<i>Macaranga tanarius</i> Müll.Arg.	Fruit, leaves	Mallotinic acid; collagin; chebulagic; macatannins A and B; nymphaeol A (6-geranyl eriodictyol); nymphaeol B (2'-geranyl eriodictyol); nymphaeol C (6-dimethylallyl-2'-geranyl eriodictyol), isonymphaeol B (5'-geranyl eriodictyol); 3'-geranyl naringenin; macatanarin D, schweinfurthin H; vedelianin; schweinfurthin F; schweinfurthin E; 4'-deprenyl-mappain; schweinfurthins K-Q; vedelianin; schweinfurthins E-G; mappain; methyl-mappain; epoxynymphaeol C; (+)-pinoselinol 4-O-[6''-O-galloyl]-beta-D-glucopyranoside; macarangiosides E and F; tanarifuranonol; tanariflavanone C; tanariflavanone D; solophenol D	Gunawan-Puteri and Kawabata (2010), Natsume et al. (2021), Marlana et al. (2018), Yoshimura et al. (2017), Syah and Ghisalberti (2015), Doan et al. (2019), Péresse et al. (2017), Syah and Ghisalberti (2015), Matsunami et al. (2009), Phommart et al. (2005), Marlana et al. (2018)
<i>Melastoma affine</i> D.Don	Leaves, flower	Auranamide; patiscabratine; α -amyrin; quercetin; kaempferol-3-O-(2aEuro(3),6aEuro(3)-di-O- <i>p-trans</i> -coumaroyl)-beta-glucoside; naringenin; kaempferol; kaempferol-3-O-D-glucoside, kaempferol-3-O-(2'', 6''-di-O- <i>p-trans</i> -coumaroyl) glucoside and kaempferol-3-O-D-glucoside	Sirat et al. (2010), Susanti et al. (2007)
<i>Merremia tridentata</i> (L.) Hallier f.	Stem, root	Apigenin; cosmosin; quercitrin; cynaroside	Vo Van et al. (2022)

Table 6 continued

Species	Part studied	Isolated compounds	References
<i>Morinda citrifolia</i> L.	Fruit, stem	<i>trans</i> -(3 <i>E</i>)-3-(3,4-dihydroxybenzylidene)-5-(3,4-dihydroxyphenyl)-4-(hydroxymethyl)dihydrofuran-2(3 <i>H</i>)-one; (–)-3,4,3',4'-tetrahydroxy-9,7' β -epoxylignan-7 β ,9'-lactone; (7 <i>R</i> ,8 <i>R</i>)-3-methoxy-1'-carboxy-4',7'-epoxy-8,3'-oxynolignan-4,9-diol; (–)-3,4,3',4'-tetrahydroxy-9,7' α -epoxylignan-7 α ,9'-lactone; (7 <i>R</i> ,8 <i>R</i>)-3,4,9-trihydroxy-4',7'-epoxy-8,3'-oxynolignan-1'-al; (7 <i>E</i>), (7 <i>R</i> ,8 <i>S</i>)-3,4,9-trihydroxy-4',7'-epoxy-8,3'-oxynolignan-7'-en-8'-oic acid; ursolic acid; episesamin 2,6-dicatechol; (–)-3,3'-bisdemethylpinosresinol, (–)-pinosresinol; lirioreosinol B; lirioreosinol B dimethyl ether; americanin A; arteminorin D; rel-(7 α ,8 β)-3-methoxy-4',7'-epoxy-8,3'-oxynolignan-4,9,9'-triol; americanic acid A; methyl 3-(2,4-dihydroxy-5-methoxyphenyl)propionate; butyl 3-(2,4-dihydroxy-5-methoxyphenyl)propionate; 5-hydroxyhexyl 2-hydroxypropanoate; morindicinone (= 2-hydroxy-1,8-dimethoxy-7-methoxymethylanthraquinone); morindicinone (= 4-hydroxymethyl-1,3-dimethoxyanthraquinone); 2-hydroxyanthraquinone; 2-methoxyanthraquinone; asperulosidic acid; rutin; nonioside A; (2 <i>E</i> ,4 <i>E</i> ,7 <i>Z</i>)-deca-2,4,7-trienoate-2-O- β -D-glucopyranosyl- β -D-glucopyranoside; triceitin	Nguyen et al. (2013), Wang et al. (2011), Siddiqui et al. (2006), Lee et al. (2020)
<i>Ocimum gratissimum</i> L.	Leaves	l-Caftaric acid; l-chioric acid; eugenyl- β -D-glucopyranoside; vicenin-2; oleanolic acid; ursolic acid; acetate of oleanolic acid; pomolic acid; tormentic acid; xanthomicrol; β -sitosterol; stigmasterol	Casanova et al. (2014), Nganteng et al. (2022)
<i>Ocimum tenuiflorum</i> L.	Leaves	2-(4-Hydroxy-3-methoxyphenyl)-8-methoxy-6-prop-2-enyl-1,3,4-dihydro-2H-chromen-3-ol; dehydrodieugenol B	Ranteh et al. (2024), Dandekar et al. (2021)
<i>Pandanus tectorius</i> Parkinson	Fruit, leaves, aerial root	(<i>Z</i>)-4-Hydroxy-3-(4-hydroxy-3-methylbut-2-en-1-yl) benzaldehyde; <i>p</i> -hydroxybenzaldehyde; syringaldehyde; (<i>E</i>)-ferulaldehyde; (<i>E</i>)-sinapinaldehyde; vanillin and 5-hydroxymethylfurfural; pandanusin A; bergapten; 6-(6'-hydroxy-3',7'-dimethylacta-2',7'-dienyl)-7-hydroxycoumarin; 6-(6',7'-dihydroxy-3',7'-dimethylact-2'-enyl)-7-hydroxycoumarin; (+)-syringaresinol; (+)-pinosresinol, (+)-lyoniresinol; (+)-medioresinol; (–)-balanophonin; luteolin, (<i>S</i>)-2,3-dihydroluteolin; 2,3-bis-(4-hydroxy-3-methoxyphenyl)-3-methoxypropanol; tachioside; <i>p</i> -hydroxycinnamaldehyde; 1-O-(28-hydroxyoctacosanoyl)glycerol; methyl β -D-fructopyranoside; (8 <i>S</i> , 8' <i>S</i>)-2,2',3,3'-tetramethoxy-4'-hydroxy-epoxylignan-4-O- β -D-glucoside; 2,20,3,30-tetramethoxy-40-hydroxy-epoxylignan-4-O- β -D-glucoside; 2,20,3,30-dimethoxy-4,80-oxynoligna-9,40,70,90-tetraol-7(8)-ene 1; (7 <i>S</i> , 8 <i>R</i>)-4,7,9,90-tetrahydroxy-3,30-dimethoxy-8-O-40-neolignan; (<i>p</i>)-isolaricresinol; 4,40-dimethoxy-30-hydroxy-7,90,70,9-diepoxy lignan-3-O- β -D-glucopyranoside; (<i>p</i>)-syringaresinol-O- β -D-glucopyranoside; (7 <i>R</i> , 8 <i>R</i>)-4,7,9,90-tetrahydroxy-3,30-dimethoxy-8-O-40-neolignan, secoisolaricresinol; 2-methoxy-4-methylphenyl 1-O-rutinoside; 3,5-dimethoxy-4-hydroxyphenyl 1-O-rutinoside and (<i>S</i>)-2-hydroxy-2-phenylethyl 1-O-rutinoside; 2-methoxy-4-hydroxymethylphenyl 1-O-rutinoside; cuneataside D; benzyl rutinoside;	Mai et al. (2015), Nguyen et al. (2016), Zhu and Zhang (2022), Sahakitpichan et al. (2020)

Table 6 continued

Species	Part studied	Isolated compounds	References
<i>Syzygium cumini</i> (L.) Skeels	Leaves, bark, seed	Syzygiate A and B; dipropyl succinate; dioctyl phthalate; friedelin; mycaminose; N-(1-azabicyclo[2.2.2]octan-3-yl)-2-(6,7-dimethoxy-2-methyl-4-oxo-3,4-dihydroquinazolin-3-yl)acetamide; 6-amino-2-((1-[2-amino-3-(1H-indol-3-yl)propanoyl]pyrrolidin-2-yl)formamido)hexanoic acid; (2,2,6,6-tetramethylpiperidin-4-yl) 12-hydroxyoctadecanoate; 2-(docosanoylamino)-3-methylbutanoic acid; 4-carbamoyl-2-dodecylhexadecanoic acid; maslinic acid; 5-(hydroxymethyl) furfural; gallic acid; valoneic acid dilactone; rubuphenol; ellagic acid; flavopiridol; kaempferol; quercetin 3-O- α -L-rhamnopyranoside; rhamnoside; kaempferol 3-O- β -D-glucuronopyranoside; myricetin 3-O- β -D-glucuronopyranoside; mearnsin 3-O-(4''-O-acetyl)- α -L-rhamnopyranoside; lupeol; 7-hydroxycalamene, gallic acid; syzygiate A and B; dipropyl succinate; dioctyl phthalate	Mujawah et al. (2023), Ghosh et al. (2024), Sawant et al. (2015), Aung et al. (2020), Sahab et al. (2023)
<i>Terminalia catappa</i> L.	Stem bark, leaves, fruit	3,4,5-Trimethoxyphenyl-1-O-(4-sulfo)-beta-D-glucopyranoside; chebuloside arjunoglucoside II; arjunolic acid; 3-betulinic acid; sitosterol-3-O-beta-D-glucopyranoside	Pertuit et al. (2015)
<i>Ziziphus oenoplia</i> (L.) Mill.	Root	Ziziphine N-Q	Suksamrarn et al. (2005)

standard GP- α inhibitor caffeine (IC_{50} = 457.34 μ M), and its α -glucosidase inhibitory activity (IC_{50} = 26.41 μ M) was 5.5 times greater than that of standard drug acarbose (IC_{50} = 145.83 μ M) (Abdulwali Ablat et al. 2017). The compounds isolated from *Pandanus tectorius*, namely, (Z)-4-hydroxy-3-(4-hydroxy-3-methylbut-2-en-1-yl) benzaldehyde (**2**), *p*-hydroxybenzaldehyde (**3**), syringaldehyde (**4**) (*E*-ferulaldehyde (**5**), (*E*)-sinapinaldehyde (**6**), vanillin (**7**) and 5-hydroxymethylfurfural (**8**), showed better α -glucosidase inhibitory activity (IC_{50} values ranging from 36.5 to 192.4 μ M) than acarbose (IC_{50} = 214.5 μ M) (Mai et al. 2015). Isolated compounds from the fruit of *Macaranga tanarius* were investigated for their mode of action on immortalised rat skeletal (L6) myoblast cell line. The L6 myoblast cell line is frequently utilised in vitro diabetic model system as due to its ability to differentiate into multinucleated myotubes and express proteins such as GLUT4. Isonymphaeol B (**15**) and 3'-geranyl naringenin (**16**) dose-dependently increased glucose uptake. These results suggest that compounds (**15**) and (**16**) positively affect glucose metabolism through the AMPK and GLUT1 pathways (Fig. 7) (Natsume et al. 2021).

Viscosol (**9**) from *Dodonaea viscosa*, improved insulin secretion and insulin resistance in high-fat diet (HFD)- and low-dose streptozotocin (STZ)-induced T2D mouse models (Table 4) (Sohail et al. 2022). Chicoric acid (**10**) (3 mg/kg bw), isolated from *Ocimum gratissimum*, also significantly decreased the blood glucose levels of diabetic mice by 53% at 120 min after treatment (Table 4) (Casanova et al. 2014). Alpha-amyrin acetate (**11**) (100 mg/kg bw), which was isolated from the fruits of *F. racemosa*, reduced blood glucose levels by 18.4% and 17.0% at 5 and 24 h, respectively, in a sucrose-challenged STZ-induced diabetic rat model (Narender et al. 2009; Mujawah et al. 2023).

Two compounds isolated from the seed extract of *Syzigium cumini*, mycaminose (**12**) and cuminoside (**13**) (50 mg/kg bw each), were evaluated for their antidiabetic properties in STZ-induced diabetic rats. Both compounds were able to significantly reduce blood glucose levels ($p < 0.05$) (Kumar et al. 2008). Additionally, these compounds significantly decreased the levels of triglyceride, low-density lipoprotein (LDL), cholesterol, and hepatic enzymes such as lactate dehydrogenase (LDH), alanine

aminotransferase (ALT), and aspartate aminotransferase (AST) in diabetic rats, while there was increased in high-density lipoprotein (HDL) level (Farswana et al. 2009). Gossypin (**14**), isolated from *Hibiscus vitifolius*, enhanced glucose tolerance and significantly normalised blood glucose, plasma insulin, and HbA1c levels after oral treatment in diabetic rats (Venkatesan and Sorimuthu Pillai 2012). Additionally, gossypin also increased glycogen levels and normalised blood urea and plasma protein levels. The efficacy of gossypin was comparable to that of a standard antidiabetic drug gliclazide (Venkatesan and Sorimuthu Pillai 2012).

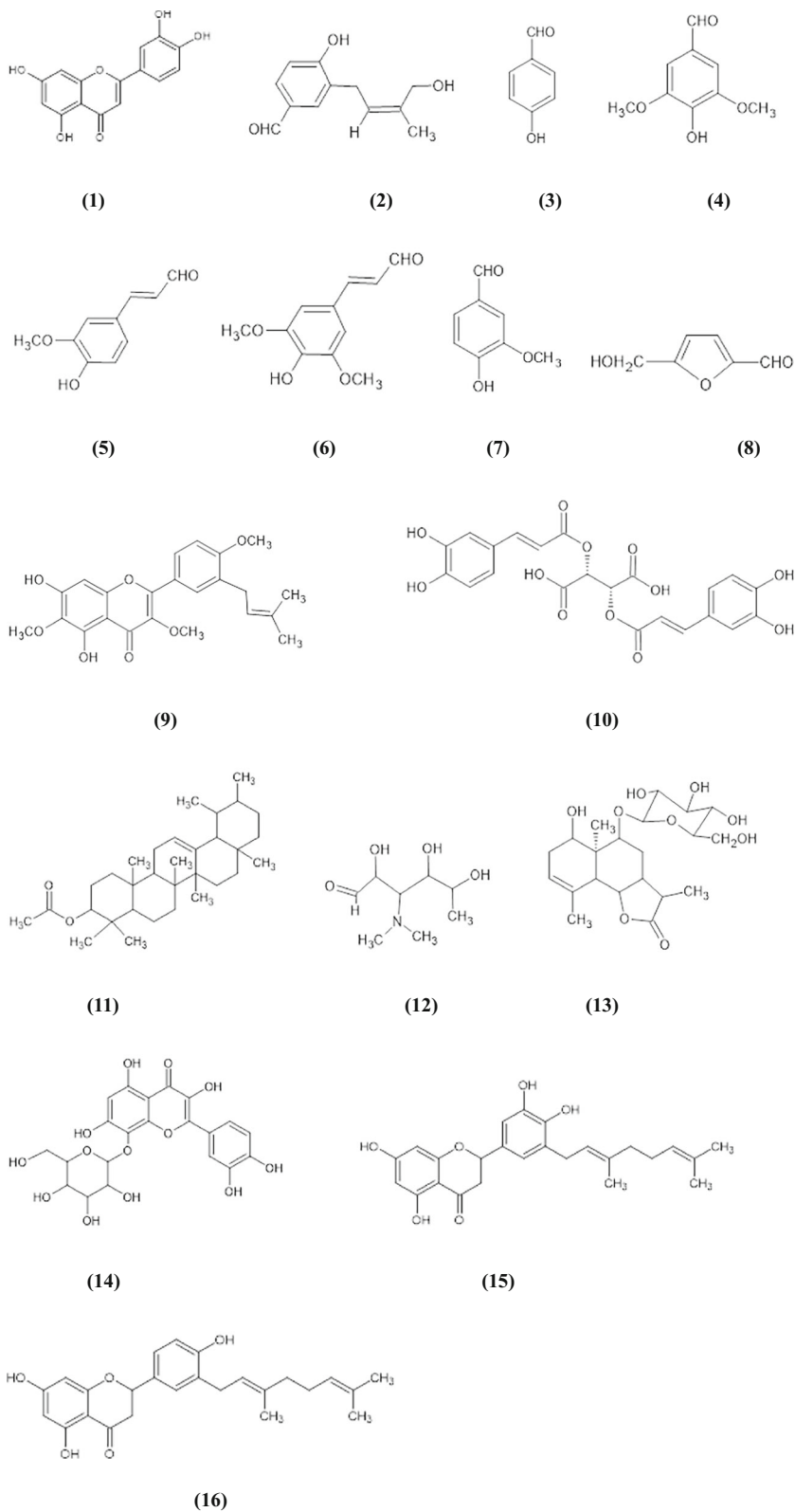
Strategies for the biodiscovery of antidiabetic molecules

1. Techniques for the isolation and characterisation of antidiabetic compounds

The antidiabetic compounds from medicinal plants are obtained through bioassay-guided isolation techniques, as illustrated in Fig. 8. The plant materials were dried and powdered before extraction and fractionation. Polar solvents such as methanol, water, and ethanol (with various concentrations ranging from 50 to 96%) are commonly used for extraction, followed by fractionation with solvents of different polarities: *n*-hexane or petroleum ether (nonpolar), chloroform, or ethyl acetate (semipolar) and butanol (polar) (Laxman Sawant et al. 2015; Parasuraman et al. 2015; Masoongnoen et al. 2022). The most bioactive extracts or fractions identified via high-throughput in vitro screening, including cytotoxicity and antidiabetic assays, are selected for further isolation and characterisation of pure small molecules.

Isolation techniques use either Sephadex column chromatography (CC) with gradient elution from less polar to polar solvents or reverse-phase high-performance liquid chromatography (RP-HPLC), the most widely used HPLC method, where the stationary phase is less polar than the eluting solvent (Laxman Sawant et al. 2015; Ablat et al. 2017; Susanti et al. 2024). The purity of isolated compounds is confirmed using analytical high-performance liquid chromatography (HPLC) or conventional thin-layer chromatography (TLC). The approximate mass (m/z) of the isolated compounds are determined via liquid chromatography-mass spectrometry (LC-MS). Advanced high-

Fig. 7 Chemical structures of antidiabetic lead compounds identified via in vitro assays (**1–8**) and in vivo experimental animal models (**9–16**). Structures were drawn via ChemSketch ADC/Labs software



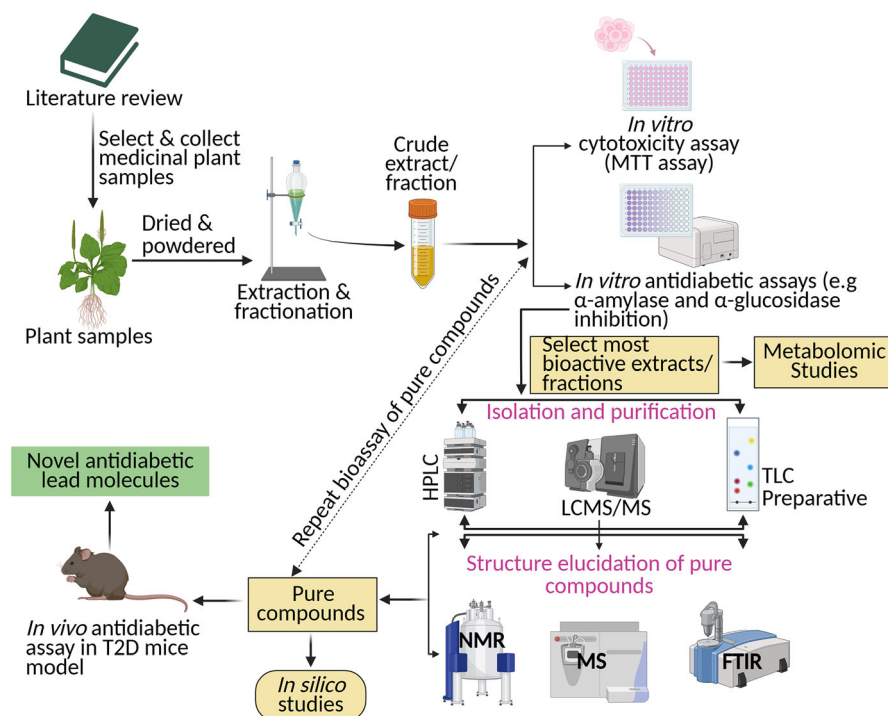


Fig. 8 Bioassay-guided isolation of novel antidiabetic lead molecules (Kabubii et al. 2024; Phukhatmuen et al. 2020)

resolution mass spectrometry (HRMS) enables the determination of the exact mass (m/z) of an isolated compound as a new natural product (Abirami Natara-jan et al. 2015). Nuclear magnetic resonance (NMR) spectroscopy, including 1D NMR (^1H and ^{13}C NMR) and various 2D NMR experiments (HSQC, HMBC, NOESY, and TOCSY) are used to derive spectroscopic data to elucidate the chemical structure of isolated compounds (Dong et al. 2024). The antidiabetic properties of isolated and identified compounds are evaluated using appropriate in vitro assays and/or in vivo model systems to identify antidiabetic lead molecules.

2. Approaches for screening crude extracts or isolated compounds for their antidiabetic properties

From this literature review, three approaches were used for screening antidiabetic properties, namely, in vitro, in vivo, and in silico, to discover antidiabetic lead molecules from medicinal plants. In in vitro screening assays, the effects of test compounds on metabolic enzymes, especially α -amylase and α -glucosidase, were compared with those of standard

compounds, such as acarbose (Hayaza et al. 2019, Vo Van et al. 2022). These enzymes are the key enzymes linked to T2D and play important roles in glucose production and carbohydrate digestion processes. The inhibition of these enzymes has become an important strategy in blood glucose management (Obboh et al. 2014; Hamden et al. 2013).

Diabetic animal models such as mice, rats, and rabbits were commonly used in in vivo testing. Diabetic condition was induced with a high-fat diet feeds or chemically using alloxan, streptozotocin, nicotinamide, or a combination of two or more inducers before the treatment. The hypoglycemic effect was then assessed by measuring the diabetic parameters such as decrease in fasting blood glucose levels, hemoglobin A1c (HbA1c), or glucose tolerance with reference to standard drugs such as glibenclamide and metformin. Other parameters assessed are pancreas histology and insulin level, triglycerides, low- and high-density lipoprotein (LDL and HDL), cholesterol, and hepatic enzymes. In addition to in vitro and in vivo methods, in silico method was also used to study the antidiabetic activities of compounds through molecular docking and binding affinities to specific

proteins. For example, 7-deoxy-6-epi-castanospermine, isolated from *Castanospermum australe* seeds, was a strong DPP-IV inhibitor comparable to berberine (Sudhanshu Kumar Bharti et al. 2012). Docking studies have shown that (4Z, 12Z)-cyclopentadeca-4,12-dienone, isolated from the leaves of *Grewia hirsuta*, effectively targets various diabetes-related sites (Abirami Natarajan et al. 2015; Abirami and Natarajan 2014).

Conclusion and future directions

In summary, this review identified 126 species of Australian tropical medicinal plants used by Australian Aboriginal people as folk medicines to treat wounds and diabetes-related conditions. These plants (126 species) belong to 47 families and 88 genera, of which Myrtaceae was the dominant family. The plant lifeforms were mostly shrubs, and the leaves were the most used plant parts. Among the 126 species, 28 were edible, and fruits were the most consumed by Aboriginal people. Crude plant extracts from 29 species have been tested for their antidiabetic properties through in vitro and/or in vivo assays to scientifically validate their ethnopharmacological uses. Among those species, crude extracts of *Syzygium cumini*, and *Morinda citrifolia* were the most widely studied for their antidiabetic activities. Furthermore, *Morinda citrifolia* extract and a combination of *Eleocharis dulcis* and *Brassica rapa* have been tested clinically in diabetic patients. A total of 374 compounds have been isolated from 26 species, of which 51 have been tested in vitro and/or in vivo for their antidiabetic properties. As a result, 16 compounds were identified as promising antidiabetic drug leads.

Australian tropical medicinal plants offer a natural and sustainable source of antidiabetic compounds, which have long been utilised in traditional treatments for diabetes-related conditions and hold a significant cultural importance for Indigenous communities. These plants are rich in diverse phytochemicals with potential health benefits, presenting promising opportunities for diabetes management through the development of drugs and nutraceuticals. However, limited research on many of these plants poses a challenge to their acceptance in mainstream medicine. Additionally, variability in plant extracts can lead to

inconsistent study results, making it difficult to obtain approval for new treatments derived from these plants.

There are many challenges in utilising medicinal plants directly for antidiabetic treatments. Ensuring the consistent quality and potency of plant extracts and conducting rigorous clinical trials to validate their efficacy and safety are the main hurdles. It is also essential to identify lead antidiabetic compounds in these bioactive plant extracts, investigate their mechanisms of action and compare their efficacy with that of conventional antidiabetic drugs. Ethical considerations must be addressed by respecting the intellectual property and traditional knowledge of indigenous communities to foster collaboration among researchers, traditional healers, and indigenous communities. Advanced techniques such as genomics and metabolomics can be also employed to gain a deeper understanding of the bioactive compounds in these plants. Integrating these medicinal plants, including their crude extracts and purified compounds into clinical practice will require well-designed clinical trials and regulatory approval.

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Declaration

Competing interest All authors declare no competing interest.

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