plants

MDPI

Review

Antidiabetic Potential of Plants from the Caribbean Basin

Vanessa Méril-Mamert [1,†], Alejandro Ponce-Mora [2,†], Muriel Sylvestre [1], Genica Lawrence [1], Eloy Bejarano [2,*] and Gerardo Cebrián-Torrejón [1,*]

[1] Laboratoire COVACHIM-M2E EA 3592, Université des Antilles, CEDEX, 97157 Pointe-à-Pitre, France; vanessa.mamert@etu.univ-antilles.fr (V.M.-M.); muriel.sylvestre@univ-antilles.fr (M.S.); genica.lawrence@univ-antilles.fr (G.L.)

[2] Department of Biomedical Sciences, School of Health Sciences and Veterinary, Universidad Cardenal Herrera-CEU, CEU Universities, 46113 Moncada, Spain; alejandro.poncemora1@uchceu.es

* Correspondence: eloy.bejaranofernandez@uchceu.es (E.B.); gerardo.cebrian-torrejon@univ-antilles.fr (G.C.-T.); Tel.: +96-136-90-00 (ext. 64541) (E.B.); +96-136-90-00 (ext. 64315) (G.C.-T.)

† These authors contributed equally to this work.

Abstract: Diabetes mellitus (DM) is a group of metabolic disorders characterized by hyperglycemia, insulin insufficiency or insulin resistance, and many issues, including vascular complications, glycative stress and lipid metabolism dysregulation. Natural products from plants with antihyperglycemic, hypolipidemic, pancreatic protective, antioxidative, and insulin-like properties complement conventional treatments. Throughout this review, we summarize the current status of knowledge of plants from the Caribbean basin traditionally used to manage DM and treat its sequelae. Seven plants were chosen due to their use in Caribbean folk medicine. We summarize the antidiabetic properties of each species, exploring the pharmacological mechanisms related to their antidiabetic effect reported in vitro and in vivo. We propose the Caribbean flora as a source of innovative bioactive phytocompounds to treat and prevent DM and DM-associated complications.

Keywords: diabetes mellitus; phytocompounds; hyperglycemia; glycative stress

Citation: Méril-Mamert, V.; Ponce-Mora, A.; Sylvestre, M.; Lawrence, G.; Bejarano, E.; Cebrián-Torrejón, G. Antidiabetic Potential of Plants from the Caribbean Basin. *Plants* **2022**, *11*, 1360. https://doi.org/10.3390/plants11101360

Academic Editors: Alessandra Braca and Marinella De Leo

Received: 2 March 2022
Accepted: 20 April 2022
Published: 20 May 2022

1. Introduction

Diabetes mellitus (DM) is a chronic disturbance that occurs when the hypoglycemic hormone insulin is not released in adequate amounts or when its activity is ineffective due to metabolic resistance [1,2]. Type 1 diabetes (T1D) generally begins in puberty and is an autoimmune condition in which the loss of β cells from the pancreas leads to insufficient insulin production [1]. In type 2 diabetes (T2D), the pancreas can produce insulin, but cells from different organs (fat, liver and muscle) do not respond properly to this hormone [2]. T2D accounts for 90 percent of incidence and usually begins in adulthood [3].

DM affects a large number of people, especially in low-and middle-income countries. According to the World Health Organization (WHO), about 422 million people worldwide have DM, and 1.6 million deaths are directly linked to DM or DM-related complications [4]. Furthermore, its prevalence is expected to increase, reaching 578 million people by 2030 and 700 million people by 2045 [5]. In particular, the Caribbean region is one of the fast-growing regions in DM prevalence [6]. The economic cost directly and indirectly associated with DM management is expected to increase worldwide. It will represent a challenging burden to the health system financing of countries with a high prevalence of DM, such as the Caribbean and Latin American countries [7].

DM is a disease of metabolic dysregulation that results in the buildup of aberrant sugar levels in the bloodstream. At the molecular level, chronic hyperglycemia leads to the accumulation of toxic advanced glycation end products (AGEs). AGEs are a diverse array of compounds formed through a non-enzymatic reaction known as glycation in which sugars or sugar metabolites attach to different biomolecules, such as proteins, impairing their function. Given that glycation is a sugar concentration-dependent reaction, high levels

of glycative stress are a key pathophysiological feature in DM, being the monitorization of glycated hemoglobin A1c (HbA1c) and the most common blood test to diagnose DM [8,9]. AGE accumulation toxicity is etiologically related to multiple diabetic complications, both microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular (dyslipidemia, hypertension, stroke, and myocardial infarction). Thus, DM increases the risk of several health debilities, including fatigue, poor wound healing, or chronic organ damage [10].

Conventional anti-DM therapies include lifestyle modifications (nutrition (e.g., low-carbohydrate diets), exercise, and weight loss), oral pharmacological agents, and subcutaneous pharmaceutical insulin [11]. Oral antidiabetic agents are used as monotherapy or in combination [12] for improved blood glucose control. As a result of this polypharmacy strategy, there are multiple possible side effects described: dizziness, constipation, nausea, diarrhea, headaches, vomiting, indigestion, loss of appetite, increased sweating, weight gain, skin reactions, and hypoglycemia [13]. Many people with DM choose to combine natural products or plant extracts with their medication to mitigate these side effects. This combination might reduce their need for medication and prevent complications [14]. Thus, the usage of herbal therapies is becoming increasingly important because of their effectiveness, limiting side effects, convenient access, and fair prices. It is estimated that the prevalence of the use of plants in people with DM is increasing worldwide in ranges between 30 and 57% [15]. In this context, DM patients use 1.6 times more complementary and herbal medicine than non-diabetics [16]. In addition, over 800 plants might have promising potential against DM complications [17]. Only a few plants used in conventional medicine have been phytochemically, biologically or clinically tested [18,19]. Importantly, herbal medicine also has side effects, often overlooked by the patients [20]. Therefore, more clinical research needs to help patients safely use plants.

Herbal remedies have been traditionally used to maintain general health and well-being. Given the high prevalence of DM in the population of the Caribbean basin, there is popular knowledge on medicinal plants to prevent or treat DM [21–23]. This traditional medicine takes advantage of the extraordinary biodiversity of the Caribbean islands, considered a global biodiversity hotspot [24,25]. Furthermore, food technology research is helping the scientific community to decipher new valuable information regarding the nutritional composition and the antidiabetic potential of edible plants and fruits [26,27]. In particular, this review focuses on the description of antidiabetic plants from the Caribbean basin, exploring their pharmacological mechanisms to propose the Caribbean flora as a source of innovative bioactive natural products to treat and prevent DM and associated complications. Exploring the anti-DM bibliography, we have selected 7 Caribbean plants, 5 indigenous and 2 exotic species, traditionally used in Caribbean folk medicine. In vivo and in vitro preclinical, experimental evidence of hypoglycemic influence are available (Tables 1 and 2). These seven species are *Anacardium occidentale* L. (Anacardiaceae), *Hyptis suaveolens* (L.) Poit. (Lamiaceae), *Persea americana* Mill. (Lauraceae), *Psidium guajava* L. (Myrtaceae), *Momordica charantia* L. (Cucurbitaceae), *Tecoma stans* (L.) Juss. ex Kunth (Bignoniaceae) and *Phyllanthus niruri* L. (Phyllanthaceae). We classified these plants regarding their pharmacological activity and the mechanism of action of their key active phytocomponents.

Table 1. General overview of plants from the Caribbean flora described in this review in which in vitro studies are available. Information about the origin, part of the plant used, type of extract, antidiabetic activity and references are provided.

Plant	Origin	Part Used	Extract	Activity	References
Anacardium occidentale L. (Anacardiaceae)	Indigenous	Cashew seed Cashew nuts	Hydroethanolic	Hypolipidemic	[28,29]
Hyptis suaveolens (L.) Poit. (Lamiaceae)	Indigenous	Aerial parts	Ethanolic Aqueous-ethanolic Petroleum ether Chloroform fraction	Hypoglycemic	[30]

Table 1. *Cont.*

Plant	Origin	Part Used	Extract	Activity	References
P. guajava L. (Myrtaceae)	Indigenous	Leaves Bark	Aqueous	Hypoglycemic α-amylase inhibitor α-glucosidase inhibitor Hypolipidemic Antiglycation	[31–35]
Tecoma stans (L.) Juss. ex Kunth (Bignoniaceae)	Indigenous	Leaves	Hydroalcoholic Aqueous	Antihyperlipidemic	[36,37]
Phyllanthus niruri L. (Phyllanthaceae)	Exotic	Leaves	Ethanolic Aqueous	Antihyperlipidemic Antihyperglycemic α-glucosidase inhibitor Antioxidant	[38,39]

Table 2. General overview of plants from the Caribbean flora described in this review in which in vivo studies are available. Information about the origin, part of the plant used, type of extract, antidiabetic activity and references are provided.

Plant	Origin	Part Used	Extract	Activity	References
Anacardium occidentale L. (Anacardiaceae)	Indigenous	Leaves Bark Cashew nuts	Hexane Aqueous Methanolic Ethanolic	Hypoglycemic Hypolipidemic Anti-inflammatory antioxidant	[39–44]
Hyptis suaveolens (L.) Poit. (Lamiaceae)	Indigenous	Leaves	Ethanolic Aqueous-ethanolic	Insulin-mimetism Insulin secretagogue Hypoglycemic hypolipidemic	[45,46]
Persea americana Mill (Lauraceae)	Indigenous	Leaves Fruit Seeds	Hydroalcoholic Phenolic Aqueous Ethanolic Methanolic	Hypoglycemic α-amylase inhibitor α-glucosidase inhibitor DM-associated complication protection (nephroprotection and hepatoprotection) Hypolipidemic Pancreatic protector	[47–50]
P. guajava L. (Myrtaceae)	Indigenous	Leaves	Aqueous Ethanolic	Hypoglycemic Hypolipidemic Antiglycation DM-associated complication protection (cardioprotection and nephroprotection) Antioxidant	[51–57]
Tecoma stans (L.) Juss. ex Kunth (Bignoniaceae)	Indigenous	Leaves	Aqueous	Antihyperlipidemic Antihyperglycemic antioxidant α-glucosidase inhibitor Antiglycation	[58–62]
Momordica charantia L. (Cucurbitaceae)	Exotic	Fruit	Aqueous Methanolic Ethanolic	Antihyperglycemic Antihyperlipidemic Antioxidant DM-associated complication protection (nephroprotection)	[63–69]
Phyllanthus niruri L. (Phyllanthaceae)	Exotic	Aerial parts Leaves	Ethanolic Aqueous	Antihyperlipidemic Antihyperglycemic Antiglycation DM-associated complication protection (nephroprotection) Antioxidant	[39,70,71]

2. The Caribbean Flora: A Unique and Diverse Source of Pharmacological Compounds

Many natural products isolated from plants, including polypeptides, carotenoids, flavonoids, alkaloids, terpenoids, saponins, tannins and glycosides, have previously shown antidiabetic properties [72,73]. The antidiabetic acting mechanisms of the phytochemicals found in plants can be categorized into six groups regarding their pharmacological mechanism: (I) glucose metabolism modulators, (II) hypolipidemic effectors, (III) pancreatic effectors, (IV) antioxidative effectors, (V) diabetic-related complications modulators and (VI) insulin-mimetic and insulin-sensitizer modulators [74].

The first group contains phytochemicals that modulate metabolic pathways in which glucose acts as a substrate or as a product. Therefore, they affect gluconeogenesis, glycogenolysis, pentose phosphate pathways and glycogenesis. This group is also comprised of phytochemicals that affect glucose uptake and compounds that show α-glucosidase and α-amylase inhibitory activity. Group II harbors phytochemicals that lower triglyceride levels and cholesterol content, impacting hyperlipidemia, a pathophysiological feature of DM [75]. Group III is comprised of bioactive compounds that can protect against β cell damage, increase their proliferation and stimulate insulin secretion. On the other hand, groups IV and V include phytochemicals that protect from DM-derived oxidative stress and DM-related complications. Finally, natural products that mimic and enhance insulin activity can also be found in herbal extracts (group VI). Interestingly, phytochemicals from plants can display multiple anti-DM effects. An illustrative example is a case of flavonoids that can be categorized into several groups (at least I and III) [76].

The Caribbean flora constitutes an untapped reservoir of natural biodiversity and a vast source of natural products. It has evolved under conditions of extreme environmental stress. It is exposed to multiple stressors, including high levels of UV radiation, high temperatures, anaerobic soils, strong winds, high salt and sulfide concentrations, oxidative stress, nutrient deficiency, extreme seasonality, phytopathogens and herbivory. The ability of Caribbean species to grow under these conditions is mainly due to specialized physiological processes that affect the chemical responses of the plants, triggering the biosynthesis of unique metabolites that include hydrocarbons, terpenoids, polyphenols, alkaloids, flavonoids, and quinones [77]. Several species were cited on different ethnopharmacological surveys developed by the TRAMIL network (Program of Applied Research to Popular Medicine in the Caribbean, www.tramil.net) (accessed on 28 September 2021) [78]. This multidisciplinary project aims to validate scientifically the pharmacological potential of medicinal plants used in primary care in multiple regions of the Caribbean basin. This multidisciplinary network created in the 1980s has dev eloped a research program to valorize and make available traditional knowledge of the uses of medicinal Caribbean flora and practical and affordable treatments that harmonize with the popular traditions of the Caribbean basin. The main objective of TRAMIL is to assure access to practical ethnopharmacological knowledge of the local flora, validated previously by scientific methods, for the local people, medical and paramedical staff and the academy or institutions related to environmental health conservation. Additionally, another purpose of the program is to highlight popular herbal medicine as a complementary resource to allopathic medicine and fight for the value of the Caribbean culture and ancestral traditions.

Here we summarize the available literature about the antidiabetic potential of these Caribbean species. We compile in vitro and in vivo experimental evidence supporting a beneficial impact of extracts or isolated fractions that follow the above-described antidiabetic action mechanisms (Figures 1 and 2).

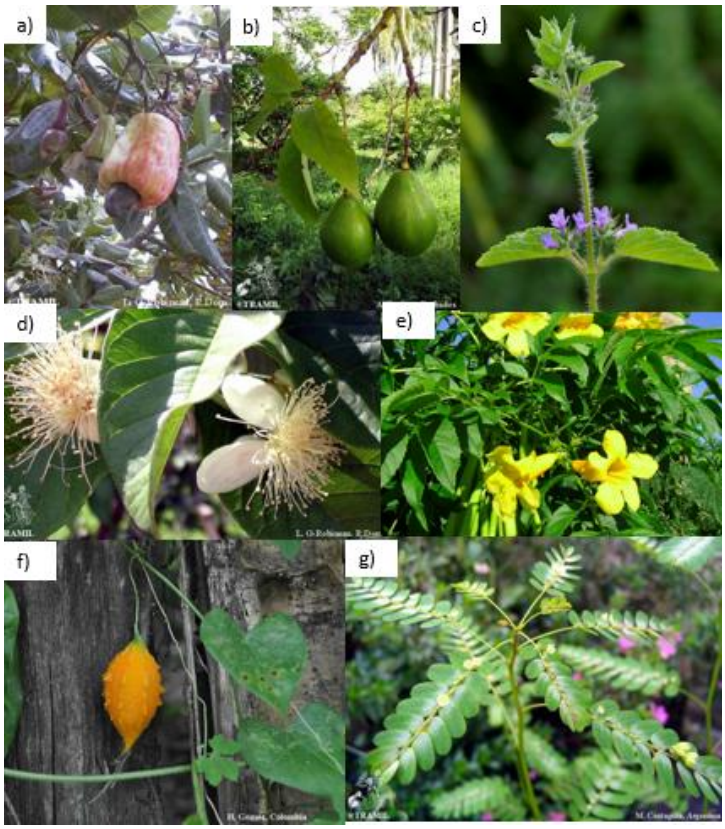

Figure 1. Representative picture of medicinal Caribbean flora discussed through the review. (**a**) *Anacardium occidentale* L., (**b**) *Hyptis suaveolens* (L.) Poit., (**c**) *Persea americana* Mill., (**d**) *Psidium guajava* L., (**e**) *Tecoma stans* (L.) Juss. ex Kunth, (**f**) *Momordica charantia* L. and (**g**) *Phyllanthus niruri* L. (source: www.tramil.net).

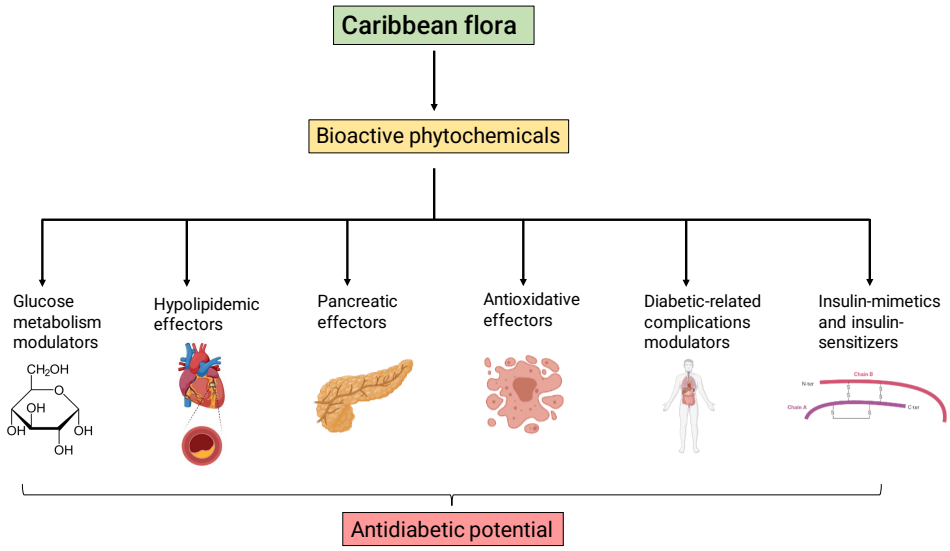

Figure 2. Hypothetical model of antidiabetic action mechanisms of bioactive phytochemicals from the Caribbean flora. Phytochemical compounds may act as glucose metabolism modulators, hypolipidemic effectors, pancreatic effectors, anti-oxidative effectors, diabetic-related complication modulators and insulin mimetics/sensitizers.

2.1. *Anacardium occidentale* L.

A. occidentale L. (Figures 1a and 3) is a tropical tree widely used for medicinal and nutraceutical purposes. Leaf, seed, and bark extracts from *A. occidentale* L. have been

shown to have antidiabetic, antibacterial, anti-inflammatory, and antiulcerogenic properties. Ethanolic extracts of *A. occidentale* stem bark and flowers contain flavones, phenolic compounds, triterpenes, xanthones, anacardic acids (AA) (e.g., 6-pentadecyl salicylic acid) and gallic acid [79]. The antidiabetic potential of *A. occidentale* is also being explored using computational approaches. According to a ligand-based prediction model, 8 different hit compounds from the plant (kaempferol 3-*O*-*β*-D-Xyloside, myricetin, quercetin-3-*O*- *β*-D-arabinofuranoside, delphinidin, gallic acid, quercetin-3-*O*-D-galactopyranoside, (+) catechin, protocatechuic acid, epigallocatechin, naringenin and (−) epicatechin) have potential action against glutamine-fructose-6-phosphate aminotransferase 1 (GFAT1) and dipeptidyl peptidase-4 (DPP-4), two promising therapeutic targets for DM management [80].

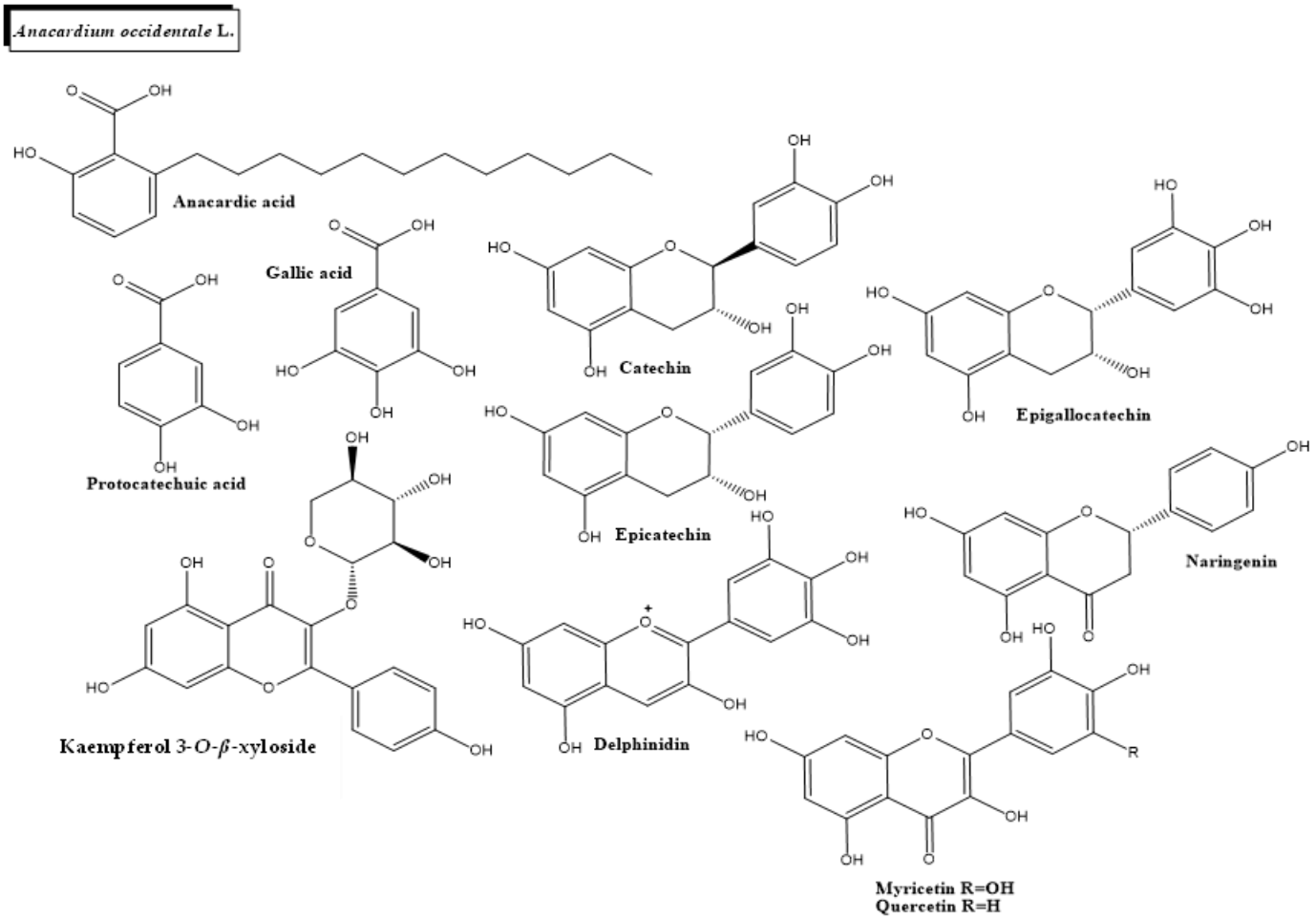

Figure 3. Chemical structures of bioactive phytocompounds with reported antidiabetic properties identified in *Anacardium occidentale* L.

Several in vivo studies strengthen the antidiabetic potential of plant extracts of *A. occidentale* [40,41,81,82]. In mice fed with a high fat and high sucrose diet, AA therapy significantly decreased serum insulin and the homeostatic model assessment of insulin resistance (HOMA-IR) levels, resulting in slightly lower liver weights and significantly lower levels of liver fats, total cholesterol, and low-density lipoprotein cholesterol [28]. The methanolic extract (100 mg/kg) of *A. occidentale* leaves had major beneficial effects in lowering blood glucose levels in streptozotocin-induced diabetic rats. The impact of *A. occidentale* extracts was similar to pioglitazone, a standard medicine used for DM management. After administration of 100 mg/kg of plant extract, the rats' blood glucose levels showed an 8.01% and 19.25% decrease in their fasting blood glucose levels after 15 and 30 days, respectively [40]. Another study reported that the aqueous extract

(175 mg/kg) of *A. occidentale* leaves showed protection against the hyperglycemic effects of streptozotocin in rats [41].

The role of AA as a therapeutic agent on metabolic disorders, including fatty liver disease and DM, has been deeply investigated. AA in vitro administration reduced lipid accumulation in 3T3-L1 cells without observed cytotoxicity. Adipocyte differentiation was inhibited by reducing the expression of the fatty acid synthase (FAS) and peroxisome proliferator-activated receptor-gamma (PPAR-γ), two adipogenesis-related markers [28]. Hydroethanolic extracts of *A. occidentale* seeds and their active ingredient, AA, induced glucose absorption into C2C12 muscle cells in a dose-dependent manner. Nonetheless, the extracts from other plant sections (leaves, bark, and apple) were inactive [29]. In addition to AA, it has been suggested that other phytocompounds of the plant extract could be responsible for its antidiabetic effect. For example, terpenoids and coumarins or stigmast-4-en-3-ol and stigmast-4-en-3-one, two steroidal compounds found in bark extracts, might have antidiabetic properties [42,43].

Compelling literature supports that, in addition to its hypoglycemic and hypolipidemic impact, *A. occidentale* might affect different antidiabetic acting mechanisms. For example, the oral administration of the ethanolic extract of *A. occidentale* flowers revealed anti-inflammatory behavior in diabetic mice with sepsis and extended mice lifespan. The flower extract of the plant stimulated the recruitment and proliferation of macrophages and neutrophils and decreased IL-6, MCP-1, and TNF-α, three immunomodulatory cytokines [83]. In a mouse model of colitis, the oral administration of cashew nuts from *A. occidentale* showed anti-inflammatory and antioxidant properties, reducing neutrophil infiltration and colon damage and lowering malondialdehyde (MDA) and pro-inflammatory cytokine levels. Additionally, cashew nut administration enhanced manganese superoxide dismutase (MnSOD) antioxidant activity and inhibited NF-kβ nuclear factor, a key player during inflammation [44]. *A. occidentale* bark extract has also been reported to stimulate pancreatic β cell islet cells. The plant extract acted on β-cells similarly to sulfonylurea drugs, stimulating insulin discharge in a glucose-dependent manner [82].

Despite many in vitro and in vivo studies using *A. occidentale* extracts, the information about its toxicity and safety is scant. Regarding the acute toxicity of the hexane leaf extract on mice, the LD_{50} was reported to be 16 g/kg. Additionally, the oral subchronic treatment during 56 days at doses of 10 and 14 g/kg suggests liver and kidney toxicity since urea, creatinine and transaminase levels are impaired [84].

Furthermore, recent findings suggest that other plants from the *Anacardiun* genus can also be used in DM management. For instance, the ethanolic extract of *Anacardium humile* St. Hil leaves showed important in vitro antiglycation and antioxidant activity. It inhibited α-amylase activity in RAW264.7 cells, a mouse macrophage cell line [85].

2.2. *Hyptis suaveolens* (L.) Poit.

H. suaveolens (L.) Poit. (Figures 1b and 4) is an aromatic medicinal plant commonly used in Central and South America and the West Indies. Due to its pharmacological potential, it has been used for multiple therapeutic purposes. Evidence suggests that *H. suaveolens* possesses anti-cancerous, antibacterial, antifungal, and antihyperglycemic activity [86].

H. suaveolens' phytochemical profile contains alkaloids, carbohydrates, flavonoids, tannins, steroids, and terpenes [86]. Other phytochemical constituents present in *H. suaveolens* leaves are hentriacontane, hentriacontanone, lupeol, diterpenoids, and triterpenoids. There is scant information about the pharmacological potential of these phytocompounds of *H. suaveolens.* The major therapeutical activity of the plant might reside in ursolic acid (UA), a pentacyclic triterpenoid. UA is a potent hypoglycemic agent acting as an insulin secretagogue and insulinomimetic. It enhances insulin secretion, transportation and uptake by the glucose transporter protein (GLU4) by stimulating the intracellular accumulation of calcium [45,87].

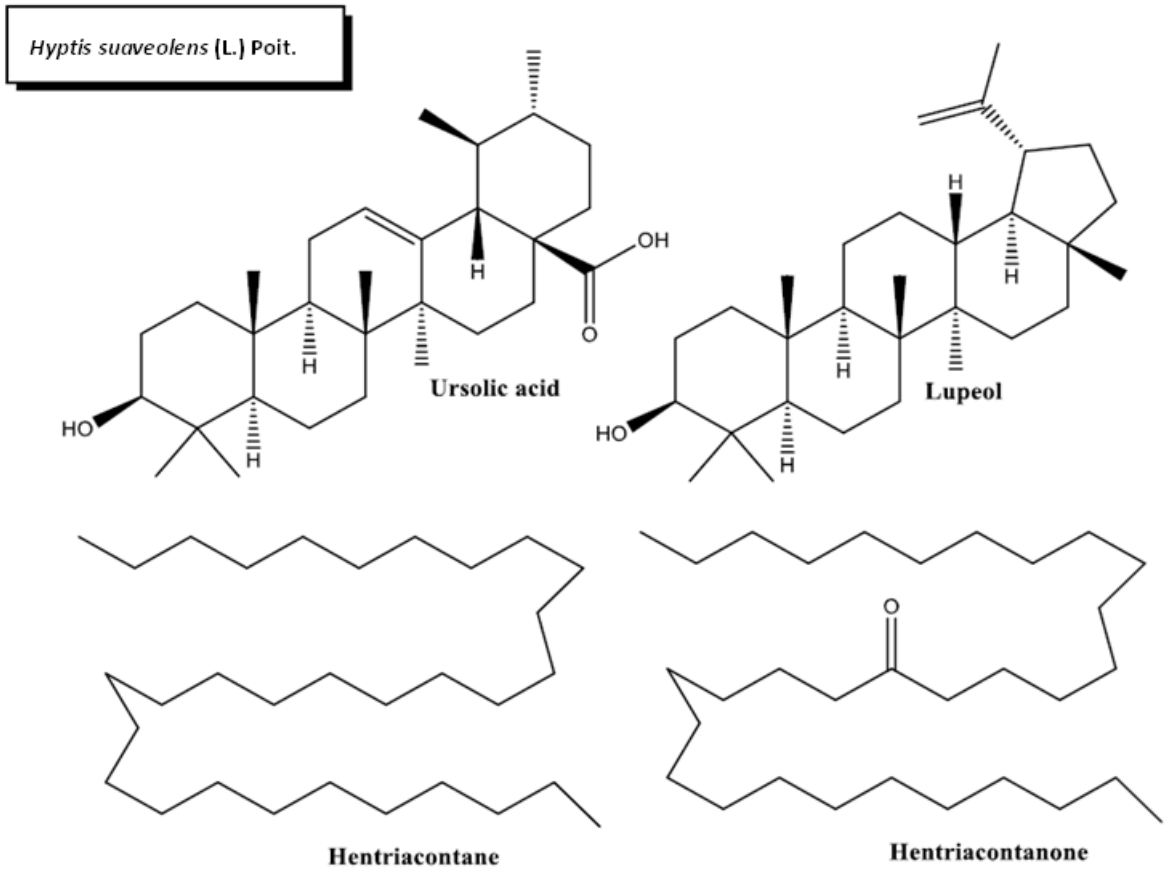

Figure 4. Chemical structures of bioactive phytocompounds with reported antidiabetic properties identified in *Hyptis suaveolens* (L.) Poit.

Growing evidence informs the promising potential of *H. suaveolens* extracts for DM management. The oral administration of the ethanolic extract of the leaves had a hypoglycemic impact in diabetic rats, also reducing cholesterol and triglyceride levels [46]. Additionally, the plant's aqueous ethanolic and petroleum ether extracts had comparable benefits to standard insulin as they significantly reduced blood glucose levels by stimulating peripheral glucose utilization [30]. The chloroform fraction of *H. suaveolens* had antioxidant potential in different diabetic rat models and inhibitory potential on salivary α-amylase [88]. These findings regarding *H. suaveolens* as an antihyperglycemic agent and for promoting the improvement of oxidative stress present this Caribbean species as a promising source of phytocompounds to fight against DM. Unfortunately, there is no information regarding *H. suaveolens'* side effects and toxicity. Further studies are needed to address its suitability for pharmaceutical purposes.

The antidiabetic potential of other plant species belonging to the *Hyptis* genus has also been tested. In streptozotocin-induced diabetic rats, the administration of the ethanolic extract of *Hyptis verticillata* jacq. leaves decreased HbA1c and fasting blood glucose levels [89]. Analogously, the ethanolic extract (250 mg/kg and 500 mg/kg) of *H. verticillata* ameliorated dyslipidemia (increasing the cardioprotective index and lowering the atherogenic coefficient and the atherogenic and coronary risk indices) [90]. The *H. verticillata* extract diminished oxidative stress (decreasing MDA and stimulating catalase, glutathione peroxidase and superoxide dismutase (SOD)) and also ameliorated hepato-renal damage and lowered blood glucose levels of streptozotocin-induced rats [90].

2.3. Persea americana Mill.

Persea americana Mill. (Figures 1c and 5) is an arboreal plant originally from Central and South America and is known for its fruit, commonly referred to as avocado. High

levels of bioactive compounds have been described in *P. americana*, including phenol compounds, organic acids, alkaloids, diterpenoids and amino acids [91]. Avocado fruit has many phytonutrients, including oleic acid, unsaturated fatty acids, palmitoleic, linoleic acid, acetogenins and carotenoids [92]. The nutraceutical richness of avocado is well known, and several metabolites of the fruit have anti-inflammatory, anticancer, antimicrobial and cardioprotective properties [93]. Among these compounds, two glycosylated flavonoids (isoquercitrin and quercetin) have a hypoglycemic effect. These molecules act by inhibiting GLUT2 (a bidirectional transmembrane passive glucose transporter) or facilitating GLUT4 (insulin-sensitive glucose transporter that facilitates glucose uptake by cells) membrane translocation [94–96].

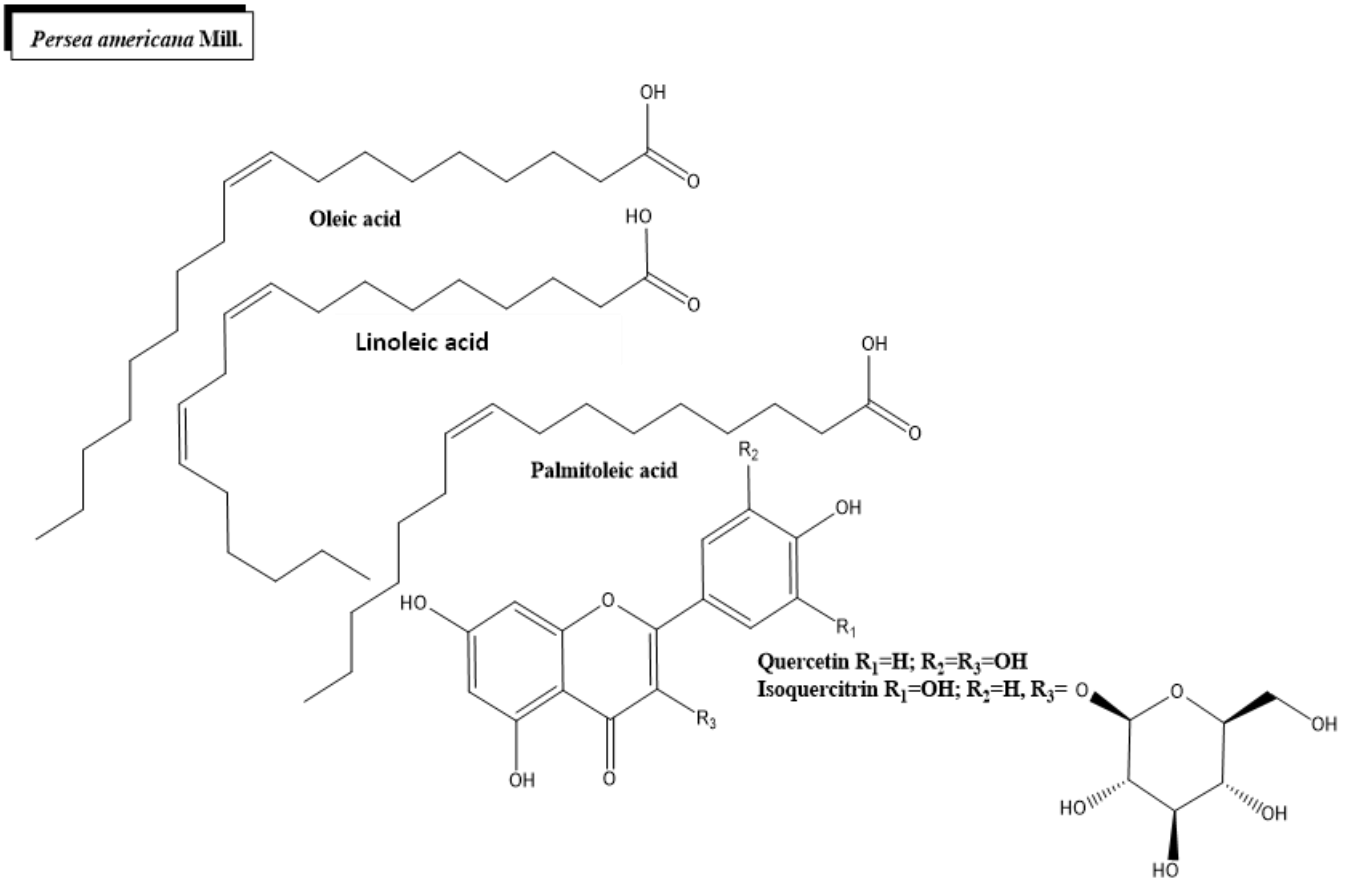

Figure 5. Chemical structures of bioactive phytocompounds with reported antidiabetic properties identified in *Persea americana* Mill.

P. americana leaves have been proposed as an interesting phytopharmaceutical source. In a comparative study, the effects of aqueous, ethanolic and methanolic leaf extracts of the plant were assessed in nicotinamide and streptozotocin-induced diabetic rats. The methanolic extract displayed the highest antidiabetic potential, but all the extracts significantly reduced glucose blood levels and ameliorated the hyperlipidemic state of the diabetic rats [47]. The authors also suggested that the hydroethanolic extract might stimulate the regeneration of the islets of Langerhans from the pancreas. In another study, the hydroalcoholic extract of *P. americana* leaves reduced blood glucose content in diabetic rats, restoring the intracellular energetic balance through the phosphorylation and the activation of protein kinase B (PKB), a central player in the AKT/PKB signaling pathway [48]. This signal transduction pathway is activated in response to insulin or growth factors and mediates multiple cell responses such as nutrient metabolism, proliferation, cell growth and apoptosis [97]. The activation of PKB promotes glyconeogenesis through glycogen

synthase activation [98]. Nevertheless, since *P. americana* leaves can modify normal renal function [99], further studies regarding their safety are needed.

P. americana seeds have also demonstrated antidiabetic effects. The oral administration of an aqueous extract of *P. americana* seeds to alloxan-induced diabetic rats had significant tissue-protective effects on the pancreas, liver, and kidney and lowered blood glucose levels. The hypoglycemic effect was similar to glibenclamide, a drug used for T2D management [49].

Additionally, *P. americana* extracts have been linked to the inhibition of T2D key enzymes. The phenolic extracts of *P. americana* leaves and fruit inhibit both α-amylase and α-glucosidase in a dose-dependent manner [50]. According to its IC_{50} value (half-maximal inhibitory concentration), the peel had the highest inhibitory activity for α-amylase, while the leaves had the most inhibitory action for α-glucosidase. Moreover, the phenolic extracts inhibited induced-lipid peroxidation in the pancreas in a dose-dependent manner [50].

Apart from *P. americana*, other plants from the *Persea* genus have shown promising antiglycation and antidiabetic properties. In alloxan-induced diabetic rabbits, 24 days of treatment with the crude extract of *Persea duthieion* reduced the animals' body weight and had significant antihyperglycemic effects. In particular, the ethyl acetate fraction of the extract had the highest antidiabetic activity [100]. Moreover, the methanolic leaf extract of *Persea indica* inhibited BSA glycation in vitro and inhibited α-amylase, α-glucosidase, and aldose reductase activity. The antiglycative action was higher than that observed for aminoguanidine, a glycation protector compound [101].

2.4. *Psidium guajava* L.

Psidium guajava L. (Figures 1d and 6) is a medicinal tree native to South America, Central America and the Caribbean. Almost every part of *P. guajava*, including its fruits, leaves, bark, and roots, has been widely used to treat or prevent DM and protein glycation and a variety of affections such as gastrointestinal disorders, cancer, inflammation, diarrhea, and hypertension [102,103].

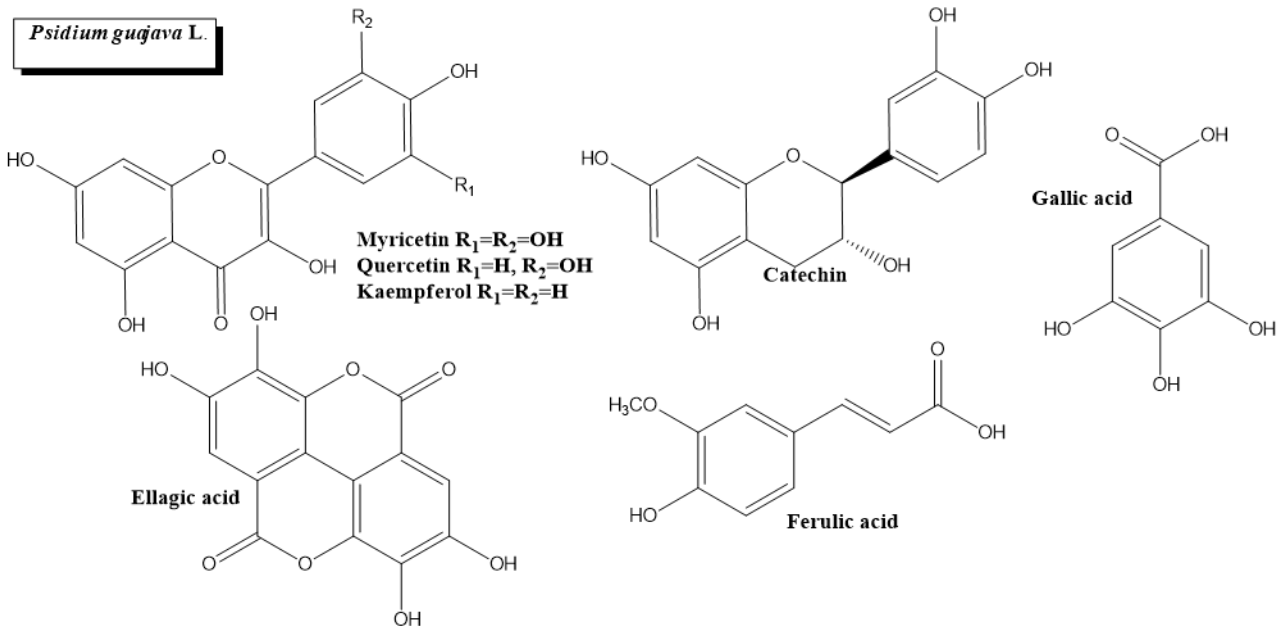

Figure 6. Chemical structures of bioactive phytocompounds with reported antidiabetic properties identified in *Psidium guajava* L.

P. guajava leaf extract contains anthraquinones and ellagic acid, two active compounds with inhibitory activities for α-amylase, tyrosinase and hyaluronidase [104]. Significant in vitro evidence supports the antidiabetic properties of *P. guajava*. Quercetin, a flavonoid

found in the leaf's aqueous extract, improved glucose absorption in cultured rat hepatocytes [105]. The ethanolic extract of *P. guajava* leaves and bark stimulated glucose uptake in murine C2C12 skeletal muscle cells and enhanced triglyceride accumulation in 3T3-L1 adipocyte-like cells [31].

The leaves of *P. guajava* have a high tannin content with a non-specific inhibitor activity of digestive enzymes, including trypsin, α-amylase, lipase and α-glucosidase. Flavonols from *P. guajava* leaves, such as myricetin, quercetin, and kaempferol, cause inhibition of maltase, α-amylase and sucrose [32,33]. Furthermore, flavonol glycosides from *P. guajava* have inhibition activity on dipeptidyl peptidase IV, a major player in glucose metabolism [106].

P. guajava has hypoglycemic consequences in many in vivo studies. The water extract of *P. guajava.* leaves lowered fasting plasma glucose, total cholesterol, low-density lipoprotein cholesterol, and glycosylated serum protein levels in vitro, reducing hyperglycemia and hyperlipidemia [51]. The oral administration of leaf *P. guajava* extracts reduced fasting blood glucose levels and increased glucose-6-phosphatase dehydrogenase, glycogen, hexokinase and insulin levels in diabetic-induced rats [52]. The authors propose that the PI3K/AKT pathway plays a major role in this hypoglycemic effect since AMPK, p-AMPK, AKT, p-AKT, IRS-1, IRS-2, PI3K and GLUT2 are activated. Another study reported that the long-term administration of aqueous and ethanolic soluble solid extracts of *P. guajava* leaves to diabetic rats improved glucose utilization and increased insulin plasma levels [53]. Interestingly, increased hepatic hexokinase, phosphofructokinase and glucose-6-phosphate dehydrogenase activity were detected in diabetic rats that were administered the aqueous extract. In contrast, in rats treated with ethanolic extract, the increment was observed only in hepatic hexokinase and glucose-6-phosphate dehydrogenase. In alignment with these results, the intraperitoneal injection of *P. guajava* extract had an antihyperglycemic activity mediated through the protein tyrosine phosphatase 1B (PTP1B), a negative regulator of the leptin and insulin signaling pathways [54]. Given that PTP1B has been proposed as a promising therapeutical target for DM and cancer [107], *P. guajava* arises as a valuable phytopharmaceutical agent. In addition, the isolated polysaccharide fraction of *P. guajava* leaves lowered the total triglyceride and cholesterol contents, decreased fasting glucose levels and enhanced the superoxide dismutase activity in streptozotocin-induced diabetic rats [55].

P. guajava leaf aqueous extract also shows a strong inhibitory effect on Amadori products (fructosamines) that are intermediates in the production of AGEs. Gallic acid, catechin and quercetin are phenolic compounds from the leaves believed to possess antiglycation properties [34]. Furthermore, ferulic acid, a phytochemical present in *P. guajava* leaf extract, shows an important antiglycative and anticoagulant activity restoring the antithrombin III function previously inhibited by methylglyoxal, a potent precursor of glycation [35].

P. guajava has also been proposed as a therapeutic agent against DM-associated complications. The plant leaf extracts' ethyl acetate fraction significantly reduced serum fructosamine and HbA1c levels. They lowered the expression of transforming growth factor β (TGF-β1), connective tissue growth factor (CTGF) and B-type natriuretic peptide (BNP) in the myocardium of diabetic rats, suggesting a cardioprotective role for the *P. guajava* extract [56]. The intraperitoneal administration of *P. guajava* triterpenoids resulted in increased serum insulin levels and insulin sensitivity index and ameliorated the renal damage of streptozotocin-induced diabetic rats [57]. These results highlight the nephroprotective potential of the plant. However, further studies are needed to evaluate the toxicity of *P. guajava* extracts since there is no information available in the literature.

2.5. Tecoma stans (L.) Juss. ex Kunth

Tecoma stans (L.) Juss. ex Kunth (Figures 1e and 7) is a flowering tree native to Central and South America. It is one of the most widely used medicinal plants for diabetes management in several countries, including the USA and Mexico [58]. Traditionally,

T. stans extracts have been used for antioxidant, analgesic, hepatoprotective, antibacterial and antiplasmodic purposes [108,109].

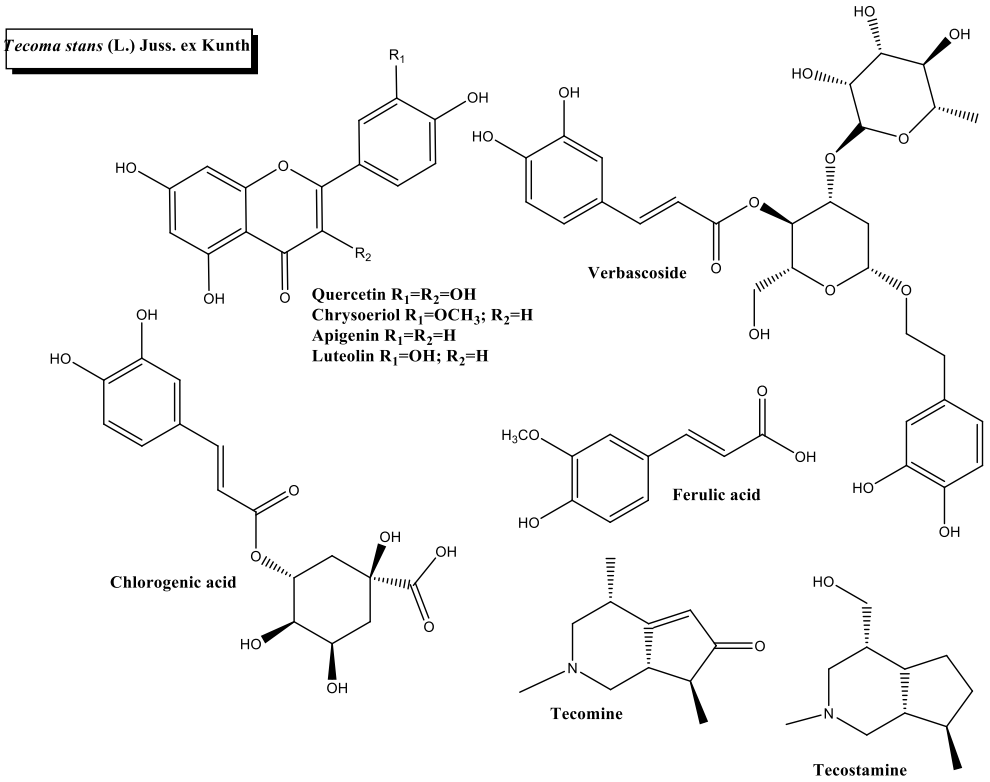

Figure 7. Chemical structures of bioactive phytocompounds with reported antidiabetic properties identified in *Tecoma stans* (L.) Juss. ex Kunth.

Approximately 120 different compounds have been isolated from *Tecoma stans* (L.) Juss. ex Kunth, including terpenoids, flavonoids, glycosides, unsaturated fatty acids and carotenoids [110]. *T. stans* produce elevated levels of phytochemical substances with pancreatic lipase inhibitory activity and, thus, antidiabetic potential. Chrysoeriol, apigenin, luteolin, and verbascoside from *T. stans* leaves showed lipase inhibitory activity, with chrysoeriol and apigenin being the most bioactive compounds [36]. Interestingly, these two phytochemicals have been linked to DM management. Chrysoeriol is a methoxyflavone that acts as an α-amylase enzyme inhibitor, and apigenin is a flavonoid with antidiabetic potential, lowering glucose blood levels, malonaldialdehyde content and insulin resistance index [59,60,111]. In addition, chlorogenic acid, tecostatine and tecomine are three phytochemicals from *T. stans* thought to have a hypoglycemic effect. Chlorogenic acid reduced postprandial peaks of glucose and decreased liver triacylglycerol levels and fasting cholesterol plasma content in obese, hyperlipidemic and insulin-resistant rats [61]. Tecomine has an in vitro hypoglycemic impact, promoting a significant stimulation of the basal uptake rate of glucose in normoglycemic rat adipocytes [112]. Tecostatine and tecostatine were proposed as hypoglycemic agents more than 70 years ago [113], although the antidiabetic effects of these compounds remain controversial.

In vivo evidence supports a beneficial effect of *T. stans* extracts in a diabetic context [58]. These exert at least four anti-diabetic properties functions, including intestinal α-glucosidase suppression, postprandial antihyperglycemic effect, hypocholesterolemic, and hypotriglyceridemic effect. Additionally, the leaf extract of *T. stans* stimulated the glucose uptake in insulin-sensitive and insulin-resistant murine or human adipocytes [37].

Recent studies report that the antidiabetic potential of *T. stans* is being examined in clinical trials. The effectiveness of an herbal mixture made of *Guazuma ulmifolia* and *T. stans* was assessed in a randomized, double-blind, placebo-controlled trial. The group of T2D

patients that were administered with the mixture showed a significant decrease in waist circumference, fasting glucose levels and HbA1c content [62]. Furthermore, the safety and toxicity of *T. stans* is a relevant issue that needs to be evaluated. The subchronic treatment with the plant extract showed no mortality and no adverse effects in rats [114].

2.6. *Momordica charantia* L.

Momordica charantia L. (Figures 1f and 8) is a health-promoting tropical plant grown in the Caribbean region, Africa and Asia. Since every part of the plant possesses therapeutical effects, it has been widely used in traditional medicine. Nevertheless, with its edible fruit, the bitter melon is one of the most-used parts for pharmacological purposes. Multiple reports show *M. charantia*'s antiobesity, antimicrobial, anti-inflammatory and anticancer properties [115–117].

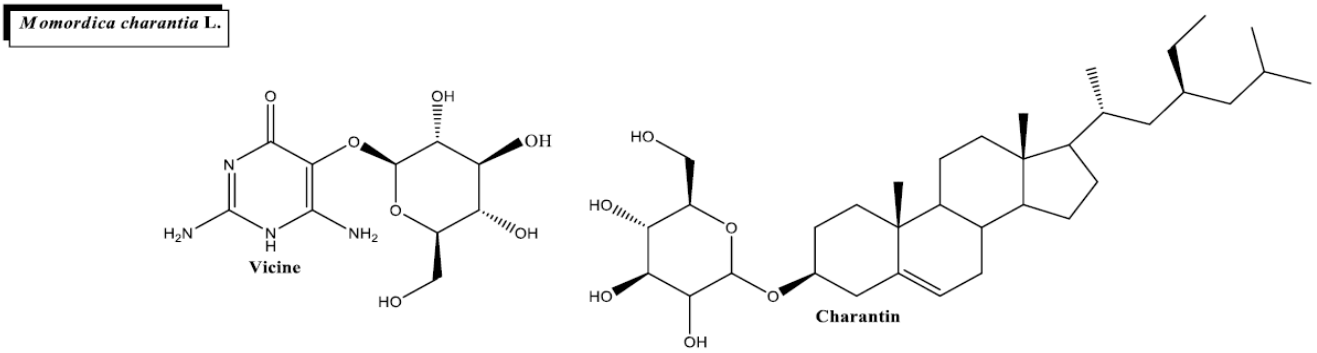

Figure 8. Chemical structures of bioactive phytocompounds with reported antidiabetic properties identified in *Momordica charantia* L.

The high richness of phytochemicals present in *M. charantia* makes this plant suitable for use in DM and DM-related complication management. *M. charantia* contains antidiabetic compounds with anti-α-glucosidase activity such as charantin, insulin-mimetic metabolites such as the polypeptide-p and insulin-sensitizing chemicals such as triterpenoids [118]. *M. charantia* also has alkaloids such as vicine, which can stimulate the uptake of cellular glucose and reduce insulin resistance [68]. Other chemicals with antidiabetic activity found in *M. charantia* include cucurbutanoid compounds, sterol glycosides and flavonoids [119]. The active components from *M. charantia* have 3 different antidiabetic mechanisms of action (as reviewed in [32]): (I) affecting the activity of glucose metabolism enzymes (enhancing glycogen synthase, glucose-6-phosphatase and glucose-6-phosphate dehydrogenase), (II) stimulating β cells from the pancreas and thus increasing insulin production and (III) serving as ligands of peroxisomal proliferator-activated receptors (PPARs), a family of receptors that regulate fat and glucose metabolism.

The hypoglycemic therapeutical effect of *M. charantia* has been tested in numerous in vivo and in vitro studies. The fruit extract showed significant antihyperglycemic activity by reducing the percentage of HbA1c and blood glucose levels and by inhibiting glycogenolysis in vitro [63]. Similarly, the oral administration of the aqueous extract of the whole fruit reduced fasting blood glucose levels in diabetic rats. It showed comparable effects to glibenclamide, a diabetic synthetic drug [64]. Additionally, the glucose tolerance curve was altered after the administration of the plant extract in several studies [65–110].

The probiotic-rich fermented extract of *M. charantia* has been proposed as a promising complementary agent for diabetes with antioxidant properties. *M. charantia* juice was fermented with *Lactobacillus fermentum* LLB3, a lactic acid bacterium, increasing its antioxidant properties [66]. In this study, streptozotocin-induced diabetic rats were fed with fermented *M. charantia* juice, non-fermented M. *charantia* juice, or administered acarbose, a typical anti-diabetic drug. The fermented juice showed more anti-diabetic properties than the non-fermented one. Rats fed with fermented juice and with non-fermented juice reported a significant reduction in fasting blood glucose levels (109.1 ± 2.07 mg/mL and

164.3 ± 2.21 mg/mL, respectively) in postprandial blood glucose levels (120.1 ± 2.49 mg/mL and 174.9 ± 2.04, respectively) mg/mL and an increase in SOD levels (61.8 ± 4.98 and 50.1 ± 5.68, respectively) when compared with diabetic rats that were given only water. However, the antidiabetic effects were lower than those observed using acarbose. Rats within this group reported the lowest fasting and postprandial blood glucose levels (88.9 ± 2.16 mg/mL and 100.4 ± 2.90 mg/mL, respectively) and the highest SOD levels (84.3 ± 3.95). In another study, the aqueous extract of the bitter melon significantly decreased blood glucose levels and HbA1c content and increased tissue glycogen serum insulin and glucagon-like peptide 1 (GLP-1) in streptozotocin-induced diabetic rats [67]. Since GLP-1 enhances insulin secretion, upregulation of GLP-1 has beneficial antidiabetic effects. In fact, GLP-1 receptor agonists are used for T2D management [120]. Furthermore, 8-week treatment using a dose of 400 mg/kg of an ethanolic *M. charantia* extract to streptozotocin-induced diabetic rats resulted in lowered serum glucose and in a reduction of the suppressor of cytokine signaling-3 (SOCS-3), c-Jun N-terminal kinase (JNK) and GLUT-4 content [121], two key players that modulate insulin resistance [122,123]. Despite the wide use of bitter melon in cuisine, it would be beneficial to characterize its use better for therapeutical purposes to prevent toxicity or possible side effects.

M. charantia can also help to prevent complications from kidney failure. A recent study showed that *M. charantia* extracts improved blood glucose levels, defended against diabetic nephropathy, decreased body weight loss, and preserved hyperglycemia in rats with streptozotocin-induced T2D [69].

2.7. *Phyllanthus niruri* L.

Phyllanthus niruri L. (Figures 1g and 9) is a perennial tropical small herb found in the coastal areas of India, in the Caribbean basin, Brasil and the Amazon rainforests. Many bioactive compounds have been identified in *P. niruri* with multiple pharmacological properties. Phytochemical research shows that the leaf extract contains alkaloids, flavonoids, saponins, tannins, lignins, terpenoids and coumarins but not hormones, glycosides or resins [124]. Due to its bioactive constituent diversity, the aerial parts of the plant have been used worldwide in traditional medicine.

Several studies highlight the anticholesterolemic, anti-inflammatory, anti-hyperuricaemic and potent anticancer and antimicrobial properties of *P. niruri* [125–127].

P. niruri has been tested as a hypoglycemic agent regarding its antidiabetic potential. The administration of the plant extract improved the lipid profile and lowered the serum glucose levels of T2D rats [70]. The authors of this study claimed that *P. niruri* protects against diabetes-related renal disorder and pointed out that this herb may be used to treat diabetic nephropathy. Another study reported that oral administration of *P. niruri* extract from its aerial parts to alloxan-induced diabetic rats lowered HbA1c, decreased blood glucose levels and increased liver glycogen amount [71].

Bioactive phytocompounds of P. niruri also enhance other antidiabetic acting mechanisms. For example, the α-glucosidase inhibitors corilagin and repandusinic acid A also have been discovered in the water extracts of *P. niruri* [38]. Additionally, the aqueous extract of the leaves was reported to have antioxidant activity and prevents AGE formation in diabetic rats [39]. The *P. niruri* extract inhibited superoxide and hydroxyl radical formation and possessed hydrogen peroxide scavenging activity by ameliorating glutathione peroxidase, catalase and superoxide dismutase function and lowering MDA and lipid peroxidation products. Unfortunately, there is no available information about *P. niruri*'s possible harmful effects. Further studies should be implemented to address the plant toxicity and dosage.

In the *Phyllanthus* genus, several other plant species have shown antidiabetic potential. An in silico study revealed that ellagic acid, phytoestrogens, sesamine, kaempferol, zeatin, quercetin, and leucodelphinidin, natural products that can be found in *Phyllanthus emblica* L. (Figure 9), possess antidiabetic activity [128]. Moreover, *Phyllanthus amarus* has reported diuretic, hypoglycemic and hypotensive effects in humans [129]. Finally, *Phyllanthus acidus*. Skeels has also shown antioxidant, hypoglycemic and α-glucosidase inhibitory activity [130].

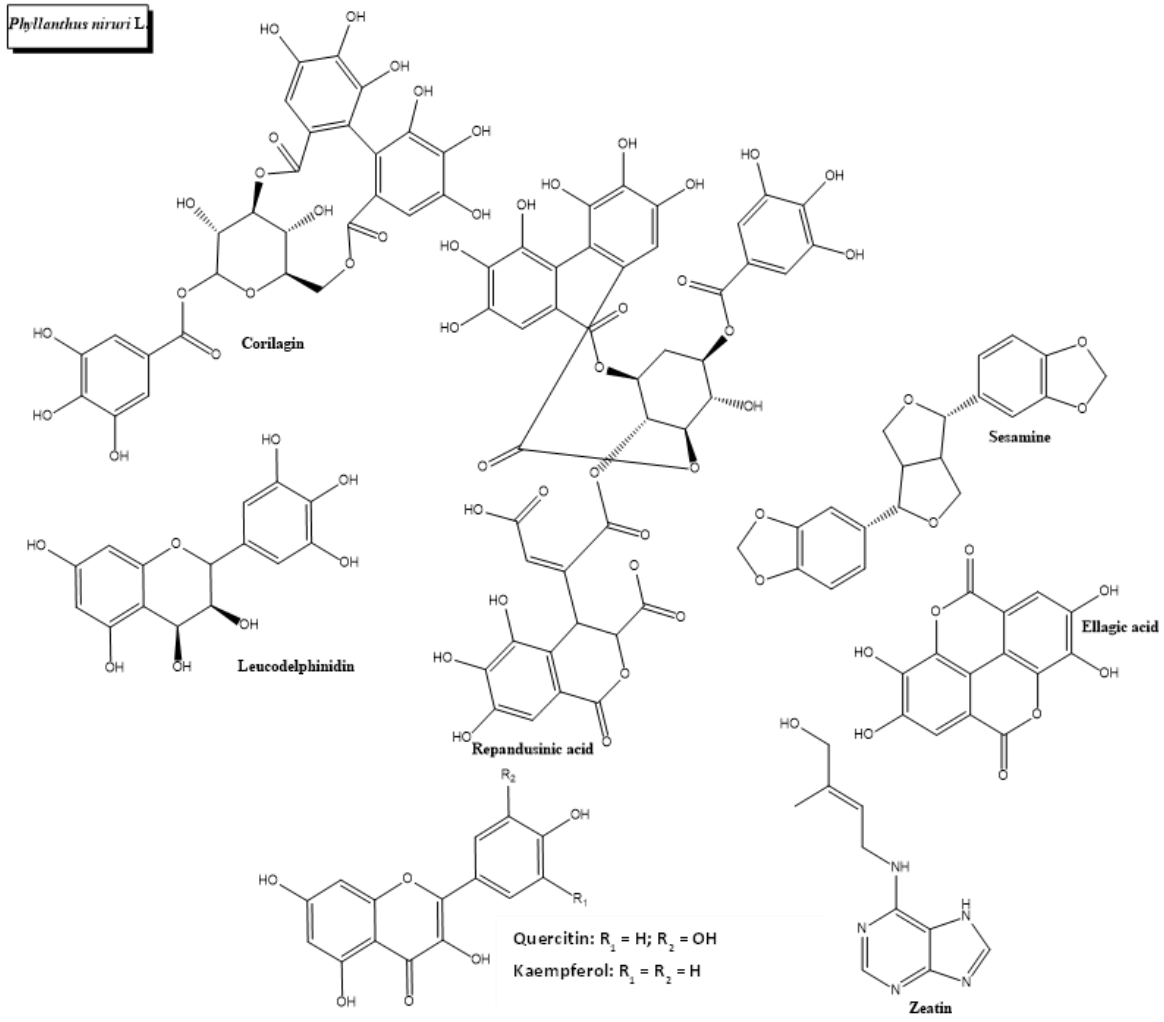

Figure 9. Chemical structures of bioactive phytocompounds with reported antidiabetic properties identified in *Phyllanthus niruri* L.

3. Conclusions and Further Perspectives

DM is a recurrent condition that calls for ongoing and long-term treatment and possesses a challenge for worldwide healthcare. In this scenario, natural products from plants represent an abundant pharmacological source to treat or prevent DM and its associated complications. A significant proportion of diabetic patients are regular users of these traditional medicines. Given that the Caribbean Basin represents a unique ethnopharmacological relevant area due to its floral diversity, the Caribbean flora represents an opportunity to discover novel bioactive phytocompounds to combat DM. This review describes the antidiabetic potential of seven widely used plants in the Caribbean region in folk medicine. However, the pharmacological information for each plant is scant. Further investigation is required to identify novel phytochemicals and determine which molecular and cellular pathways are involved in the protective anti-diabetic effect of these traditional herbal medicines. Additionally, a more intense effort in research is imperative to define the effective dosage and toxicity of the various plant extracts that are commonly used.

Author Contributions: V.M.-M., A.P.-M., E.B. and G.C.-T. contributed to the writing and editing of the original draft. M.S., G.L., E.B. and G.C.-T. designed the structure of the review and supervised the writing. All authors have read and agreed to the published version of the manuscript.

Funding: This manuscript has been supported by the European Regional Cooperation Fund Interreg Caribbean V (Project CambioNET) and grants RYC2018-024434-I, MINECO PID2020-119466RB-I00, FUSP-PPC-19-B53C4C64.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Katsarou, A.; Gudbjörnsdottir, S.; Rawshani, A.; Dabelea, D.; Bonifacio, E.; Anderson, B.J.; Jacobsen, L.M.; Schatz, D.A.; Lernmark, Å. Type 1 diabetes mellitus. *Nat. Rev. Dis. Primers* **2017**, *3*, 17016. [CrossRef] [PubMed]
2. Roden, M.; Shulman, G.I. The integrative biology of type 2 diabetes. *Nature* **2019**, *576*, 51–60. [CrossRef] [PubMed]
3. Galicia-Garcia, U.; Benito-Vicente, A.; Jebari, S.; Larrea-Sebal, A.; Siddiqi, H.; Uribe, K.B.; Ostolaza, H.; Martín, C. Pathophysiology of Type 2 Diabetes Mellitus. *Int. J. Mol. Sci.* **2020**, *21*, 6275. [CrossRef] [PubMed]
4. WHO. *Global Report on Diabetes*. 2016. Available online: http://apps.who.int/iris/bitstream/handle/10665/254648/9789241565256-fre.pdf?sequence=1 (accessed on 1 March 2022).
5. Saeedi, P.; Petersohn, I.; Salpea, P.; Malanda, B.; Karuranga, S.; Unwin, N.; Colagiuri, S.; Guariguata, L.; Motala, A.A.; Ogurtsova, K.; et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9(th) edition. *Diabetes Res. Clin. Pract.* **2019**, *157*, 107843. [CrossRef] [PubMed]
6. Gallardo-Rincón, H.; Cantoral, A.; Arrieta, A.; Espinal, C.; Magnus, M.H.; Palacios, C.; Tapia-Conyer, R. Review: Type 2 diabetes in Latin America and the Caribbean: Regional and country comparison on prevalence, trends, costs and expanded prevention. *Prim. Care Diabetes* **2021**, *15*, 352–359. [CrossRef]
7. Barcelo, A.; Arredondo, A.; Gordillo-Tobar, A.; Segovia, J.; Qiang, A. The cost of diabetes in Latin America and the Caribbean in 2015: Evidence for decision and policy makers. *J. Glob. Health* **2017**, *7*, 020410. [CrossRef]
8. Rabbani, N.; Thornalley, P.J. Glyoxalase in diabetes, obesity and related disorders. *Semin. Cell Dev. Biol.* **2011**, *22*, 309–317. [CrossRef]
9. Rabbani, N.; Xue, M.; Thornalley, P.J. Dicarbonyl stress, protein glycation and the unfolded protein response. *Glycoconj. J.* **2021**, *38*, 331–340. [CrossRef]
10. Lotfy, M.; Adeghate, J.; Kalasz, H.; Singh, J.; Adeghate, E. Chronic Complications of Diabetes Mellitus: A Mini Review. *Curr. Diabetes Rev.* **2017**, *13*, 3–10. [CrossRef]
11. Blaslov, K.; Naranđa, F.S.; Kruljac, I.; Renar, I.P. Treatment approach to type 2 diabetes: Past, present and future. *World J. Diabetes* **2018**, *9*, 209–219. [CrossRef]
12. Mudaliar, S.; Henry, R.R. Combination therapy for type 2 diabetes. *Endocr. Pract. Off. J. Am. Coll. Endocrinol. Am. Assoc. Clin. Endocrinol.* **1999**, *5*, 208–219. [CrossRef] [PubMed]
13. Salehi, B.; Ata, A.; Anil Kumar, N.V.; Sharopov, F.; Ramírez-Alarcón, K.; Ruiz-Ortega, A.; Abdulmajid Ayatollahi, S.; Tsouh Fokou, P.V.; Kobarfard, F.; Amiruddin Zakaria, Z.; et al. Antidiabetic Potential of Medicinal Plants and Their Active Components. *Biomolecules* **2019**, *9*, 551. [CrossRef] [PubMed]
14. Blahova, J.; Martiniakova, M.; Babikova, M.; Kovacova, V.; Mondockova, V.; Omelka, R. Pharmaceutical Drugs and Natural Therapeutic Products for the Treatment of Type 2 Diabetes Mellitus. *Pharmaceuticals* **2021**, *14*, 806. [CrossRef] [PubMed]
15. Bell, R.A.; Stafford, J.M.; Arcury, T.A.; Snively, B.M.; Smith, S.L.; Grzywacz, J.G.; Quandt, S.A. Complementary and Alternative Medicine Use and Diabetes Self-Management Among Rural Older Adults. *Complementary Health Pract. Rev.* **2006**, *11*, 95–106. [CrossRef] [PubMed]
16. Garrow, D.; Egede, L.E. Association between complementary and alternative medicine use, preventive care practices, and use of conventional medical services among adults with diabetes. *Diabetes Care* **2006**, *29*, 15–19. [CrossRef] [PubMed]
17. Alarcon-Aguilara, F.J.; Roman-Ramos, R.; Perez-Gutierrez, S.; Aguilar-Contreras, A.; Contreras-Weber, C.C.; Flores-Saenz, J.L. Study of the anti-hyperglycemic effect of plants used as antidiabetics. *J. Ethnopharmacol.* **1998**, *61*, 101–110. [CrossRef]
18. Farooqi, H.; Siraj, S.; Adhami, S. Unexplored Medicinal Plants of Potential Therapeutic Importance: A Review. *Trop. J. Nat. Prod. Res.* **2018**, *2*, 3–11. [CrossRef]
19. Zhang, A.L.; Xue, C.C.; Fong, H. Integration of Herbal Medicine into Evidence-Based Clinical Practice: Current Status and Issues. In *Herbal Medicine: Biomolecular and Clinical Aspects*, 2nd ed.; Benzie, I., Wachtel-Galor, S., Eds.; CRC Press/Taylor & Francis: Boca Raton, FL, USA, 2011.
20. Posadzki, P.; Watson, L.K.; Ernst, E. Adverse effects of herbal medicines: An overview of systematic reviews. *Clin. Med.* **2013**, *13*, 7–12. [CrossRef]
21. Picking, D.; Younger, N.; Mitchell, S.; Delgoda, R. The prevalence of herbal medicine home use and concomitant use with pharmaceutical medicines in Jamaica. *J. Ethnopharmacol.* **2011**, *137*, 305–311. [CrossRef]
22. Boulogne, I.; Germosén-Robineau, L.; Ozier-Lafontaine, H.; Fleury, M.; Loranger-Merciris, G. TRAMIL ethnopharmalogical survey in Les Saintes (Guadeloupe, French West Indies): A comparative study. *J. Ethnopharmacol.* **2011**, *133*, 1039–1050. [CrossRef]

23. Bahall, M.; Edwards, M. Perceptions of complementary and alternative medicine among cardiac patients in South Trinidad: A qualitative study. *BMC Complementary Altern. Med.* **2015**, *15*, 99. [CrossRef] [PubMed]
24. Santiago-Valentín, E.; Francisco-Ortega, J. Plant Evolution and Biodiversity in the Caribbean Islands–Perspectives from Molecular Markers. *Bot. Rev.* **2008**, *74*, 1–4. [CrossRef]
25. Maunder, M.; Leiva, A.; Santiago-Valentín, E.; Stevenson, D.W.; Acevedo-Rodríguez, P.; Meerow, A.W.; Mejía, M.; Clubbe, C.; Francisco-Ortega, J. Plant Conservation in the Caribbean Island Biodiversity Hotspot. *Bot. Rev.* **2008**, *74*, 197–207. [CrossRef]
26. Rana, Z.H.; Alam, M.K.; Akhtaruzzaman, M. Nutritional Composition, Total Phenolic Content, Antioxidant and α-Amylase Inhibitory Activities of Different Fractions of Selected Wild Edible Plants. *Antioxidants* **2019**, *8*, 203. [CrossRef]
27. Alam, M.K.; Rana, Z.H.; Islam, S.N. Comparison of the Proximate Composition, Total Carotenoids and Total Polyphenol Content of Nine Orange-Fleshed Sweet Potato Varieties Grown in Bangladesh. *Foods* **2016**, *5*, 64. [CrossRef]
28. Chung, S.; Shin, E.J.; Choi, H.K.; Park, J.H.; Hwang, J.T. Anacardic acid mitigates liver fat accumulation and impaired glucose tolerance in mice fed a high-fat and high-sucrose diet. *Food Sci. Nutr.* **2020**, *8*, 796–804. [CrossRef]
29. Tedong, L.; Madiraju, P.; Martineau, L.C.; Vallerand, D.; Arnason, J.T.; Desire, D.D.; Lavoie, L.; Kamtchouing, P.; Haddad, P.S. Hydro-ethanolic extract of cashew tree (*Anacardium occidentale*) nut and its principal compound, anacardic acid, stimulate glucose uptake in C2C12 muscle cells. *Mol. Nutr. Food Res.* **2010**, *54*, 1753–1762. [CrossRef]
30. Begum, A.U.; Venkatesh, S.; Prakash, J.; Alvala, R. Evaluation of glucose utilization capacity of bioactivity-guided fractions of *Barleria prionitis* Linn and *Hyptis suaveolens* (L.) Poit in isolated rat hemidiaphragm. *Ayu* **2016**, *37*, 145–150. [CrossRef]
31. Beidokhti, M.N.; Eid, H.M.; Villavicencio, M.L.S.; Jäger, A.K.; Lobbens, E.S.; Rasoanaivo, P.R.; McNair, L.M.; Haddad, P.S.; Staerk, D. Evaluation of the antidiabetic potential of *Psidium guajava* L. (Myrtaceae) using assays for α-glucosidase, α-amylase, muscle glucose uptake, liver glucose production, and triglyceride accumulation in adipocytes. *J. Ethnopharmacol.* **2020**, *257*, 112877. [CrossRef]
32. Wang, H.; Du, Y.-J.; Song, H.-C. α-Glucosidase and α-amylase inhibitory activities of guava leaves. *Food Chem.* **2010**, *123*, 6–13. [CrossRef]
33. Griffiths, D.W. The inhibition of digestive enzymes by polyphenolic compounds. *Adv. Exp. Med. Biol.* **1986**, *199*, 509–516. [CrossRef] [PubMed]
34. Wu, J.-W.; Hsieh, C.-L.; Wang, H.-Y.; Chen, H.-Y. Inhibitory effects of guava (*Psidium guajava* L.) leaf extracts and its active compounds on the glycation process of protein. *Food Chem.* **2009**, *113*, 78–84. [CrossRef]
35. Hsieh, C.-L.; Lin, Y.-C.; Yen, G.-C.; Chen, H.-Y. Preventive effects of guava (*Psidium guajava* L.) leaves and its active compounds against α-dicarbonyl compounds-induced blood coagulation. *Food Chem.* **2007**, *103*, 528–535. [CrossRef]
36. Ramirez, G.; Zamilpa, A.; Zavala, M.; Perez, J.; Morales, D.; Tortoriello, J. Chrysoeriol and other polyphenols from *Tecoma stans* with lipase inhibitory activity. *J. Ethnopharmacol.* **2016**, *185*, 1–8. [CrossRef] [PubMed]
37. Alonso-Castro, A.J.; Zapata-Bustos, R.; Romo-Yañez, J.; Camarillo-Ledesma, P.; Gómez-Sánchez, M.; Salazar-Olivo, L.A. The antidiabetic plants *Tecoma stans* (L.) Juss. ex Kunth (Bignoniaceae) and *Teucrium cubense* Jacq (Lamiaceae) induce the incorporation of glucose in insulin-sensitive and insulin-resistant murine and human adipocytes. *J. Ethnopharmacol.* **2010**, *127*, 1–6. [CrossRef]
38. Najari Beidokhti, M.; Andersen, M.V.; Eid, H.M.; Sanchez Villavicencio, M.L.; Staerk, D.; Haddad, P.S.; Jäger, A.K. Investigation of antidiabetic potential of *Phyllanthus niruri* L. using assays for α-glucosidase, muscle glucose transport, liver glucose production, and adipogenesis. *Biochem. Biophys. Res. Commun.* **2017**, *493*, 869–874. [CrossRef]
39. Giribabu, N.; Rao, P.V.; Kumar, K.P.; Muniandy, S.; Swapna Rekha, S.; Salleh, N. Aqueous Extract of *Phyllanthus niruri* Leaves Displays In Vitro Antioxidant Activity and Prevents the Elevation of Oxidative Stress in the Kidney of Streptozotocin-Induced Diabetic Male Rats. *Evid. Based Complementary Altern. Med.* **2014**, *2014*, 834815. [CrossRef]
40. Jaiswal, Y.S.; Tatke, P.A.; Gabhe, S.Y.; Vaidya, A.B. Antidiabetic activity of extracts of *Anacardium occidentale* Linn. leaves on n-streptozotocin diabetic rats. *J. Tradit. Complementary Med.* **2017**, *7*, 421–427. [CrossRef]
41. Kamtchouing, P.; Sokeng, S.D.; Moundipa, P.F.; Watcho, P.; Jatsa, H.B.; Lontsi, D. Protective role of *Anacardium occidentale* extract against streptozotocin-induced diabetes in rats. *J. Ethnopharmacol.* **1998**, *62*, 95–99. [CrossRef]
42. Ojewole, J.A. Laboratory evaluation of the hypoglycemic effect of *Anacardium occidentale* Linn (Anacardiaceae) stem-bark extracts in rats. *Methods Find. Exp. Clin. Pharmacol.* **2003**, *25*, 199–204. [CrossRef]
43. Alexander-Lindo, R.L.; Morrison, E.Y.; Nair, M.G. Hypoglycaemic effect of stigmast-4-en-3-one and its corresponding alcohol from the bark of *Anacardium occidentale* (cashew). *Phytother. Res. PTR* **2004**, *18*, 403–407. [CrossRef] [PubMed]
44. Siracusa, R.; Fusco, R.; Peritore, A.F.; Cordaro, M.; D'Amico, R.; Genovese, T.; Gugliandolo, E.; Crupi, R.; Smeriglio, A.; Mandalari, G.; et al. The Antioxidant and Anti-Inflammatory Properties of *Anacardium occidentale* L. Cashew Nuts in a Mouse Model of Colitis. *Nutrients* **2020**, *12*, 834. [CrossRef]
45. Castro, A.J.; Frederico, M.J.; Cazarolli, L.H.; Mendes, C.P.; Bretanha, L.C.; Schmidt, É.C.; Bouzon, Z.L.; de Medeiros Pinto, V.A.; da Fonte Ramos, C.; Pizzolatti, M.G. The mechanism of action of ursolic acid as insulin secretagogue and insulinomimetic is mediated by cross-talk between calcium and kinases to regulate glucose balance. *Biochim. Et Biophys. Acta* **2015**, *1850*, 51–61. [CrossRef] [PubMed]
46. Mishra, S.B.; Verma, A.; Mukerjee, A.; Vijayakumar, M. Anti-hyperglycemic activity of leaves extract of *Hyptis suaveolens* L. Poit in streptozotocin induced diabetic rats. *Asian Pac. J. Trop. Med.* **2011**, *4*, 689–693. [CrossRef]

47. Kouamé, N.M.; Koffi, C.; N'Zoué, K.S.; Yao, N.A.R.; Doukouré, B.; Kamagaté, M. Comparative Antidiabetic Activity of Aqueous, Ethanol, and Methanol Leaf Extracts of *Persea americana* and Their Effectiveness in Type 2 Diabetic Rats. *Evid. Based Complementary Altern. Med.* **2019**, *2019*, 5984570. [CrossRef] [PubMed]
48. Lima, C.R.; Vasconcelos, C.F.; Costa-Silva, J.H.; Maranhão, C.A.; Costa, J.; Batista, T.M.; Carneiro, E.M.; Soares, L.A.; Ferreira, F.; Wanderley, A.G. Anti-diabetic activity of extract from *Persea americana* Mill. leaf via the activation of protein kinase B (PKB/Akt) in streptozotocin-induced diabetic rats. *J. Ethnopharmacol.* **2012**, *141*, 517–525. [CrossRef]
49. Ezejiofor, A.N.; Okorie, A.; Orisakwe, O.E. Hypoglycaemic and tissue-protective effects of the aqueous extract of *persea americana* seeds on alloxan-induced albino rats. *Malays. J. Med. Sci.* **2013**, *20*, 31–39.
50. Oboh, G.; Isaac, A.T.; Akinyemi, A.J.; Ajani, R.A. Inhibition of key enzymes linked to type 2 diabetes and sodium nitroprusside induced lipid peroxidation in rats' pancreas by phenolic extracts of avocado pear leaves and fruit. *Int. J. Biomed. Sci* **2014**, *10*, 208–216.
51. Xu, C.; Li, X.; Zeng, D.; Liu, Y.; Gao, Y.; Tsunoda, M.; Deng, S.; Xie, X.; Wang, R.; Li, L.-S.; et al. Amino Acid Profiling Study of *Psidium guajava* L. Leaves as an Effective Treatment for Type 2 Diabetic Rats. *Evid. Based Complementary Altern. Med.* **2020**, *2020*, 9784382. [CrossRef]
52. Vinayagam, R.; Jayachandran, M.; Chung, S.S.M.; Xu, B. Guava leaf inhibits hepatic gluconeogenesis and increases glycogen synthesis via AMPK/ACC signaling pathways in streptozotocin-induced diabetic rats. *Biomed. Pharmacother.* **2018**, *103*, 1012–1017. [CrossRef]
53. Shen, S.C.; Cheng, F.C.; Wu, N.J. Effect of guava (*Psidium guajava* Linn.) leaf soluble solids on glucose metabolism in type 2 diabetic rats. *Phytother. Res.* **2008**, *22*, 1458–1464. [CrossRef] [PubMed]
54. Oh, W.K.; Lee, C.H.; Lee, M.S.; Bae, E.Y.; Sohn, C.B.; Oh, H.; Kim, B.Y.; Ahn, J.S. Antidiabetic effects of extracts from *Psidium guajava*. *J. Ethnopharmacol.* **2005**, *96*, 411–415. [CrossRef] [PubMed]
55. Luo, Y.; Peng, B.; Wei, W.; Tian, X.; Wu, Z. Antioxidant and Anti-Diabetic Activities of Polysaccharides from Guava Leaves. *Molecules* **2019**, *24*, 1343. [CrossRef] [PubMed]
56. Soman, S.; Rajamanickam, C.; Rauf, A.A.; Madambath, I. Molecular mechanisms of the antiglycative and cardioprotective activities of *Psidium guajava* leaves in the rat diabetic myocardium. *Pharm. Biol.* **2016**, *54*, 3078–3085. [CrossRef]
57. Kuang, Q.T.; Zhao, J.J.; Ye, C.L.; Wang, J.R.; Ye, K.H.; Zhang, X.Q.; Wang, Y.; Ye, W.C. Nephro-protective effects of total triterpenoids from *Psidium guajava* leaves on type 2 diabetic rats. *Zhong Yao Cai Zhongyaocai J. Chin. Med. Mater.* **2012**, *35*, 94–97.
58. Aguilar-Santamaría, L.; Ramírez, G.; Nicasio, P.; Alegría-Reyes, C.; Herrera-Arellano, A. Antidiabetic activities of *Tecoma stans* (L.) Juss. ex Kunth. *J. Ethnopharmacol.* **2009**, *124*, 284–288. [CrossRef]
59. Salehi, B.; Venditti, A.; Sharifi-Rad, M.; Kręgiel, D.; Sharifi-Rad, J.; Durazzo, A.; Lucarini, M.; Santini, A.; Souto, E.B.; Novellino, E.; et al. The Therapeutic Potential of Apigenin. *Int. J. Mol. Sci.* **2019**, *20*, 1305. [CrossRef]
60. Ren, B.; Qin, W.; Wu, F.; Wang, S.; Pan, C.; Wang, L.; Zeng, B.; Ma, S.; Liang, J. Apigenin and naringenin regulate glucose and lipid metabolism, and ameliorate vascular dysfunction in type 2 diabetic rats. *Eur. J. Pharmacol.* **2016**, *773*, 13–23. [CrossRef]
61. Rodriguez de Sotillo, D.V.; Hadley, M. Chlorogenic acid modifies plasma and liver concentrations of: Cholesterol, triacylglycerol, and minerals in (fa/fa) Zucker rats. *J. Nutr. Biochem.* **2002**, *13*, 717–726. [CrossRef]
62. Pascoe-González, S.; Ramos-Zavala, M.G.; Buenrostro Ahued, M.A.; Hernández-González, S.O.; Cardona-Muñoz, E.G.; García-Benavides, L.; Grover-Páez, F. Administration of Herbarium Mixture (*Guazuma ulmifolia*/*Tecoma stans*) on Metabolic Profile in Type 2 Diabetes Mellitus Patients: A Randomized, Double-Blind, Placebo-Controlled Trial. *J. Med. Food* **2021**, *24*, 527–532. [CrossRef]
63. Fernandes, N.P.; Lagishetty, C.V.; Panda, V.S.; Naik, S.R. An experimental evaluation of the antidiabetic and antilipidemic properties of a standardized *Momordica charantia* fruit extract. *BMC Complementary Altern. Med.* **2007**, *7*, 29. [CrossRef] [PubMed]
64. Virdi, J.; Sivakami, S.; Shahani, S.; Suthar, A.C.; Banavalikar, M.M.; Biyani, M.K. Antihyperglycemic effects of three extracts from *Momordica charantia*. *J. Ethnopharmacol.* **2003**, *88*, 107–111. [CrossRef]
65. Chaturvedi, P.; George, S.; Milinganyo, M.; Tripathi, Y.B. Effect of *Momordica charantia* on lipid profile and oral glucose tolerance in diabetic rats. *Phytother. Res.* **2004**, *18*, 954–956. [CrossRef] [PubMed]
66. Hartajanie, L.; Fatimah-Muis, S.; Heri-Nugroho Hs, K.; Riwanto, I.; Sulchan, M. Probiotics Fermented Bitter Melon Juice as Promising Complementary Agent for Diabetes Type 2: Study on Animal Model. *J. Nutr. Metab.* **2020**, *2020*, 6369873. [CrossRef] [PubMed]
67. Bhat, G.A.; Khan, H.A.; Alhomida, A.S.; Sharma, P.; Singh, R.; Paray, B.A. GLP-I secretion in healthy and diabetic Wistar rats in response to aqueous extract of *Momordica charantia*. *BMC Complementary Altern. Med.* **2018**, *18*, 162. [CrossRef] [PubMed]
68. Saeed, F.; Sultan, M.T.; Riaz, A.; Ahmed, S.; Bigiu, N.; Amarowicz, R.; Manea, R. Bitter Melon (*Momordica charantia* L.) Fruit Bioactives Charantin and Vicine Potential for Diabetes Prophylaxis and Treatment. *Plants* **2021**, *10*, 730.
69. Offor, U.; Edwin, C.S.N.; Ogedengbe, O.O.; Jegede, A.I.; Peter, A.I.; Onyemaechi, O.A. Renal histopathological and biochemical changes following adjuvant intervention of *Momordica charantia* and antiretroviral therapy in diabetic rats. *Iran. J. Basic Med. Sci.* **2019**, *22*, 1359–1367. [CrossRef] [PubMed]
70. Mediani, A.; Abas, F.; Maulidiani, M.; Khatib, A.; Tan, C.P.; Ismail, I.S.; Shaari, K.; Ismail, A.; Lajis, N.H. Metabolic and biochemical changes in streptozotocin induced obese-diabetic rats treated with *Phyllanthus niruri* extract. *J. Pharm. Biomed. Anal.* **2016**, *128*, 302–312. [CrossRef]

71. Okoli, C.O.; Obidike, I.C.; Ezike, A.C.; Akah, P.A.; Salawu, O.A. Studies on the possible mechanisms of antidiabetic activity of extract of aerial parts of *Phyllanthus niruri*. *Pharm. Biol.* **2011**, *49*, 248–255. [CrossRef]
72. Moreno-Valdespino, C.A.; Luna-Vital, D.; Camacho-Ruiz, R.M.; Mojica, L. Bioactive proteins and phytochemicals from legumes: Mechanisms of action preventing obesity and type-2 diabetes. *Food Res. Int.* **2020**, *130*, 108905. [CrossRef]
73. Li, R.; Zhang, Y.; Rasool, S.; Geetha, T.; Babu, J.R. Effects and Underlying Mechanisms of Bioactive Compounds on Type 2 Diabetes Mellitus and Alzheimer's Disease. *Oxidative Med. Cell. Longev.* **2019**, *2019*, 8165707. [CrossRef] [PubMed]
74. Chan, C.H.; Ngoh, G.C.; Yusoff, R. A brief review on anti diabetic plants: Global distribution, active ingredients, extraction techniques and acting mechanisms. *Pharmacogn. Rev.* **2012**, *6*, 22–28. [CrossRef] [PubMed]
75. Nelson, A.J.; Nicholls, S.J. Treating Dyslipidemia in Type 2 Diabetes. *Cardiol. Clin.* **2018**, *36*, 233–239. [CrossRef] [PubMed]
76. Middleton, E., Jr.; Kandaswami, C.; Theoharides, T.C. The effects of plant flavonoids on mammalian cells: Implications for inflammation, heart disease, and cancer. *Pharmacol. Rev.* **2000**, *52*, 673–751.
77. Dahibhate, L.N.; Saddhe, A.A.; Kumar, K. Mangrove Plants as a Source of Bioactive Compounds: A Review. *Nat. Prod. J.* **2019**, *9*, 86–97. [CrossRef]
78. Durán, R.; Cebrián-Torrejón, G.; Nossin, E.; Gómez-Estrada, H.; Costaguta, M. Medicina popular y atención primaria de la salud (APS): 35 años de experiencia TRAMIL en el Caribe. *Steviana* **2021**, *10*, 41–47.
79. Salehi, B.; Gültekin-Özgüven, M.; Kirkin, C.; Özçelik, B.; Morais-Braga, M.F.B.; Carneiro, J.N.P.; Bezerra, C.F.; da Silva, T.G.; Coutinho, H.D.M.; Amina, B.; et al. Antioxidant, Antimicrobial, and Anticancer Effects of Anacardium Plants: An Ethnopharmacological Perspective. *Front. Endocrinol.* **2020**, *11*, 295. [CrossRef]
80. Ukwenya, V.O.; Adelakun, S.A.; Elekofehinti, O.O. Exploring the antidiabetic potential of compounds isolated from *Anacardium occidentale* using computational aproach: Ligand-based virtual screening. *Silico Pharmacol.* **2021**, *9*, 25. [CrossRef]
81. Okpashi, V.E.; Bayim, B.P.; Obi-Abang, M. Comparative Effects of Some Medicinal Plants: *Anacardium occidentale, Eucalyptus globulus*, *Psidium guajava*, and *Xylopia aethiopica* Extracts in Alloxan-Induced Diabetic Male Wistar Albino Rats. *Biochem. Res. Int.* **2014**, *2014*, 203051. [CrossRef]
82. Singh, R. Antihyperglycemic effect of ethanolic extract and fractions of *anacardium occidentale* L. Stem bark in streptozotocin-induced diabetic rats. *J. Basic Clin. Pharm.* **2009**, *1*, 16–19.
83. Oliveira, A.S.; Nascimento, J.R.; Trovão, L.O.; Alves, P.C.S.; Maciel, M.C.G.; Silva, L.D.M.; Marques, A.A.; Santos, A.; Silva, L.A.; Nascimento, F.R.F.; et al. The anti-inflammatory activity of *Anacardium occidentale* L. increases the lifespan of diabetic mice with lethal sepsis. *J. Ethnopharmacol.* **2019**, *236*, 345–353. [CrossRef] [PubMed]
84. Tédong, L.; Dzeufiet, P.D.; Dimo, T.; Asongalem, E.A.; Sokeng, S.N.; Flejou, J.F.; Callard, P.; Kamtchouing, P. Acute and subchronic toxicity of *Anacardium occidentale* Linn (Anacardiaceae) leaves hexane extract in mice. *Afr. J. Tradit. Complementary Altern. Med. AJTCAM* **2006**, *4*, 140–147. [CrossRef] [PubMed]
85. Lima Júnior, J.P.; Franco, R.R.; Saraiva, A.L.; Moraes, I.B.; Espindola, F.S. *Anacardium humile* St. Hil as a novel source of antioxidant, antiglycation and α-amylase inhibitors molecules with potential for management of oxidative stress and diabetes. *J. Ethnopharmacol.* **2021**, *268*, 113667. [CrossRef] [PubMed]
86. Mishra, P.; Sohrab, S.; Mishra, S.K. A review on the phytochemical and pharmacological properties of *Hyptis suaveolens* (L) Poit. *Future J. Pharm. Sci.* **2021**, *7*, 65. [CrossRef]
87. Seo, D.Y.; Lee, S.R.; Heo, J.W.; No, M.H.; Rhee, B.D.; Ko, K.S.; Kwak, H.B.; Han, J. Ursolic acid in health and disease. *Korean J. Physiol. Pharmacol.* **2018**, *22*, 235–248. [CrossRef] [PubMed]
88. Nayak, P.; Kar, D.M.; Nayak, S. In Vitro α-Amylase Inhibition and Antioxidant potential of Chloroform Fraction of Hydroalcoholic Extract Obtained from *Hyptis Suaveolens*. *J. App. Pharm. Sci.* **2014**, *4*, 046–051. [CrossRef]
89. Ogar, I.; Egbung, G.E.; Nna, V.U.; Iwara, I.A.; Itam, E. Anti-hyperglycemic potential of *Hyptis verticillata* jacq in streptozotocin-induced diabetic rats. *Biomed. Pharmacother.* **2018**, *107*, 1268–1276. [CrossRef]
90. Ogar, I.; Egbung, G.E.; Nna, V.U.; Atangwho, I.J.; Itam, E.H. *Hyptis verticillata* attenuates dyslipidaemia, oxidative stress and hepato-renal damage in streptozotocin-induced diabetic rats. *Life Sci.* **2019**, *219*, 283–293. [CrossRef]
91. Bhuyan, D.J.; Alsherbiny, M.A.; Perera, S.; Low, M.; Basu, A.; Devi, O.A.; Barooah, M.S.; Li, C.G.; Papoutsis, K. The Odyssey of Bioactive Compounds in Avocado (*Persea americana*) and Their Health Benefits. *Antioxidants* **2019**, *8*, 426. [CrossRef]
92. Salazar-López, N.J.; Domínguez-Avila, J.A.; Yahia, E.M.; Belmonte-Herrera, B.H.; Wall-Medrano, A.; Montalvo-González, E.; González-Aguilar, G.A. Avocado fruit and by-products as potential sources of bioactive compounds. *Food Res. Int.* **2020**, *138*, 109774. [CrossRef]
93. Ochoa-Zarzosa, A.; Báez-Magaña, M.; Guzmán-Rodríguez, J.J.; Flores-Alvarez, L.J.; Lara-Márquez, M.; Zavala-Guerrero, B.; Salgado-Garciglia, R.; López-Gómez, R.; López-Meza, J.E. Bioactive Molecules from Native Mexican Avocado Fruit (*Persea americana* var. drymifolia): A Review. *Plant Foods Hum. Nutr.* **2021**, *76*, 133–142. [CrossRef] [PubMed]
94. Kwon, O.; Eck, P.; Chen, S.; Corpe, C.P.; Lee, J.H.; Kruhlak, M.; Levine, M. Inhibition of the intestinal glucose transporter GLUT2 by flavonoids. *FASEB J.* **2007**, *21*, 366–377. [CrossRef] [PubMed]
95. Rey, D.; Fernandes, T.A.; Sulis, P.M.; Gonçalves, R.; Sepúlveda, R.M.; Silva Frederico, M.J.; Aragon, M.; Ospina, L.F.; Costa, G.M.; Silva, F. Cellular target of isoquercetin from *Passiflora ligularis* Juss for glucose uptake in rat soleus muscle. *Chem. Biol. Interact.* **2020**, *330*, 109198. [CrossRef] [PubMed]

96. Jimenez, P.; Garcia, P.; Quitral, V.; Vasquez, K.; Parra-Ruiz, C.; Reyes-Farias, M.; Garcia-Diaz, D.F.; Robert, P.; Encina, C.; Soto-Covasich, J. Pulp, Leaf, Peel and Seed of Avocado Fruit: A Review of Bioactive Compounds and Healthy Benefits. *Food Rev. Int.* **2021**, *37*, 619–655. [CrossRef]
97. Hanada, M.; Feng, J.; Hemmings, B.A. Structure, regulation and function of PKB/AKT–a major therapeutic target. *Biochim. Et Biophys. Acta* **2004**, *1697*, 3–16. [CrossRef]
98. Zdychová, J.; Komers, R. Emerging role of Akt kinase/protein kinase B signaling in pathophysiology of diabetes and its complications. *Physiol. Res.* **2005**, *54*, 1–16.
99. Gondwe, M.; Kamadyaapa, D.R.; Tufts, M.A.; Chuturgoon, A.A.; Ojewole, J.A.; Musabayane, C.T. Effects of *Persea americana* Mill (Lauraceae) ["Avocado"] ethanolic leaf extract on blood glucose and kidney function in streptozotocin-induced diabetic rats and on kidney cell lines of the proximal (LLCPK1) and distal tubules (MDBK). *Methods Find. Exp. Clin. Pharmacol.* **2008**, *30*, 25–35. [CrossRef]
100. Sultan, K.; Zakir, M.; Khan, H.; Khan, I.U.; Ayaz, S.; Khan, I.; Khan, J.; Khan, M.A. Antihyperglycemic effect of *Persea duthieion* blood glucose levels and body weight in alloxan induced diabetic rabbits. *Pak. J. Pharm. Sci.* **2016**, *29*, 837–842.
101. Spínola, V.; Castilho, P.C. Assessing the In Vitro Inhibitory Effects on Key Enzymes Linked to Type-2 Diabetes and Obesity and Protein Glycation by Phenolic Compounds of Lauraceae Plant Species Endemic to the Laurisilva Forest. *Molecules* **2021**, *26*, 2023. [CrossRef]
102. Correa, M.G.; Couto, J.S.; Teodoro, A.J. Anticancer Properties of *Psidium guajava*—A Mini-Review. *Asian Pac. J. Cancer Prev.* **2016**, *17*, 4199–4204.
103. Hirudkar, J.R.; Parmar, K.M.; Prasad, R.S.; Sinha, S.K.; Jogi, M.S.; Itankar, P.R.; Prasad, S.K. Quercetin a major biomarker of *Psidium guajava* L. inhibits SepA protease activity of *Shigella flexneri* in treatment of infectious diarrhoea. *Microb. Pathog.* **2020**, *138*, 103807. [CrossRef]
104. Ahmed, M.H.; Aldesouki, H.M.; Badria, F.A. Effect of phenolic compounds from the leaves of *Psidium guajava* on the activity of three metabolism-related enzymes. *Biotechnol. Appl. Biochem.* **2021**, *68*, 497–512. [CrossRef] [PubMed]
105. Cheng, F.C.; Shen, S.C.; Wu, J.S. Effect of guava (*Psidium guajava* L.) leaf extract on glucose uptake in rat hepatocytes. *J. Food Sci.* **2009**, *74*, H132–H138. [CrossRef] [PubMed]
106. Eidenberger, T.; Selg, M.; Krennhuber, K. Inhibition of dipeptidyl peptidase activity by flavonol glycosides of guava (*Psidium guajava* L.): A key to the beneficial effects of guava in type II diabetes mellitus. *Fitoterapia* **2013**, *89*, 74–79. [CrossRef] [PubMed]
107. Combs, A.P. Recent advances in the discovery of competitive protein tyrosine phosphatase 1B inhibitors for the treatment of diabetes, obesity, and cancer. *J. Med. Chem.* **2010**, *53*, 2333–2344. [CrossRef] [PubMed]
108. Bakr, R.O.; Fayed, M.A.A.; Salem, M.A.; Hussein, A.S. *Tecoma stans*: Alkaloid Profile and Antimicrobial Activity. *J. Pharm. Bioallied Sci.* **2019**, *11*, 341–347. [CrossRef] [PubMed]
109. Marzouk, M.; Gamal-Eldeen, A.; Mohamed, M.; El-Sayed, M. Anti-proliferative and antioxidant constituents from *Tecoma stans*. *Zeitschrift fur Naturforschung C J. Biosci.* **2006**, *61*, 783–791.
110. Anand, M.; Basavaraju, R. A review on phytochemistry and pharmacological uses of *Tecoma stans* (L.) Juss. ex Kunth. *J. Ethnopharmacol.* **2021**, *265*, 113270. [CrossRef]
111. Nickavar, B.; Abolhasani, L. Bioactivity-Guided Separation of an α-Amylase Inhibitor Flavonoid from *Salvia virgata*. *Iran. J. Pharm. Res.* **2013**, *12*, 57–61.
112. Constantino, L.; Raimondi, L.; Pirisino, R.; Brunetti, T.; Pessotto, P.; Giannessi, F.; Lins, A.P.; Barlocco, D.; Antolini, L.; El-Abady, S.A. Isolation and Pharmacological Activities of the Tecoma Stans Alkaloids. *Farmaco* **2003**, *58*, 781–785. [CrossRef]
113. Hammouda, Y.; Rashid, A.K.; Amer, M.S. hypoglycaemic properties of tecomine and tecostanine. *J. Pharm. Pharmacol.* **1964**, *16*, 833–834. [CrossRef] [PubMed]
114. Larbie, C.; Owusu Nyarkoh, C.; Owusu Adjei, C. Phytochemical and Safety Evaluation of Hydroethanolic Leaf Extract of *Tecoma stans* (L.) Juss. ex Kunth. *Evid. Based Complementary Altern. Med.* **2019**, *2019*, 7417624. [CrossRef] [PubMed]
115. Fan, M.; Kim, E.K.; Choi, Y.J.; Tang, Y.; Moon, S.H. The Role of *Momordica charantia* in Resisting Obesity. *Int. J. Environ. Res. Public Health* **2019**, *16*, 3251. [CrossRef] [PubMed]
116. Chan, D.W.; Yung, M.M.; Chan, Y.S.; Xuan, Y.; Yang, H.; Xu, D.; Zhan, J.B.; Chan, K.K.; Ng, T.B.; Ngan, H.Y. MAP30 protein from *Momordica charantia* is therapeutic and has synergic activity with cisplatin against ovarian cancer in vivo by altering metabolism and inducing ferroptosis. *Pharmacol. Res.* **2020**, *161*, 105157. [CrossRef] [PubMed]
117. Lee, S.Y.; Wong, W.F.; Dong, J.; Cheng, K.-K. *Momordica charantia* Suppresses Inflammation and Glycolysis in Lipopolysaccharide-Activated RAW264.7 Macrophages. *Molecules* **2020**, *25*, 3783. [CrossRef] [PubMed]
118. Raman, A.; Lau, C. Anti-diabetic properties and phytochemistry of *Momordica charantia* L. (Cucurbitaceae). *Phytomedicine Int. J. Phytother. Phytopharm.* **1996**, *2*, 349–362. [CrossRef]
119. Harinantenaina, L.; Tanaka, M.; Takaoka, S.; Oda, M.; Mogami, O.; Uchida, M.; Asakawa, Y. *Momordica charantia* constituents and antidiabetic screening of the isolated major compounds. *Chem. Pharm. Bull.* **2006**, *54*, 1017–1021. [CrossRef]
120. Tran, K.L.; Park, Y.I.; Pandya, S.; Muliyil, N.J.; Jensen, B.D.; Huynh, K.; Nguyen, Q.T. Overview of Glucagon-Like Peptide-1 Receptor Agonists for the Treatment of Patients with Type 2 Diabetes. *Am. Health Drug Benefits* **2017**, *10*, 178–188.
121. Ma, C.; Yu, H.; Xiao, Y.; Wang, H. *Momordica charantia* extracts ameliorate insulin resistance by regulating the expression of SOCS-3 and JNK in type 2 diabetes mellitus rats. *Pharm. Biol.* **2017**, *55*, 2170–2177. [CrossRef]

122. Torisu, T.; Sato, N.; Yoshiga, D.; Kobayashi, T.; Yoshioka, T.; Mori, H.; Iida, M.; Yoshimura, A. The dual function of hepatic SOCS3 in insulin resistance in vivo. *Genes Cells Devoted Mol. Cell. Mech.* **2007**, *12*, 143–154. [CrossRef]
123. Li, H.; Yu, X. Emerging role of JNK in insulin resistance. *Curr. Diabetes Rev.* **2013**, *9*, 422–428. [CrossRef] [PubMed]
124. Kaur, N.; Kaur, B.; Sirhindi, G. Phytochemistry and Pharmacology of Phyllanthus niruri L.: A Review. *Phytother. Res.* **2017**, *31*, 980–1004. [CrossRef] [PubMed]
125. Sharma, P.; Parmar, J.; Verma, P.; Sharma, P.; Goyal, P.K. Anti-tumor activity of *Phyllanthus niruri* (a medicinal plant) on chemical-induced skin carcinogenesis in mice. *Asian Pac. J. Cancer Prev.* **2009**, *10*, 1089–1094. [PubMed]
126. Lee, S.H.; Jaganath, I.B.; Wang, S.M.; Sekaran, S.D. Antimetastatic effects of Phyllanthus on human lung (A549) and breast (MCF-7) cancer cell lines. *PLoS ONE* **2011**, *6*, e20994. [CrossRef] [PubMed]
127. Murugaiyah, V.; Chan, K.L. Mechanisms of antihyperuricemic effect of *Phyllanthus niruri* and its lignan constituents. *J. Ethnopharmacol.* **2009**, *124*, 233–239. [CrossRef] [PubMed]
128. Sharma, P.; Joshi, T.; Joshi, T.; Chandra, S.; Tamta, S. In silico screening of potential antidiabetic phytochemicals from *Phyllanthus emblica* against therapeutic targets of type 2 diabetes. *J. Ethnopharmacol.* **2020**, *248*, 112268. [CrossRef] [PubMed]
129. Srividya, N.; Periwal, S. Diuretic, hypotensive and hypoglycaemic effect of *Phyllanthus amarus*. *Indian J. Exp. Biol.* **1995**, *33*, 861–864.
130. Tan, S.P.; Tan, E.N.; Lim, Q.Y.; Nafiah, M.A. *Phyllanthus acidus* (L.) Skeels: A review of its traditional uses, phytochemistry, and pharmacological properties. *J. Ethnopharmacol.* **2020**, *253*, 112610. [CrossRef]