Review

New Insights into the Latest Advancement in α-Amylase Inhibitors of Plant Origin with Anti-Diabetic Effects

Hamdy Kashtoh and Kwang-Hyun Baek *

Department of Biotechnology, Yeungnam University, Gyeongsan 38541, Republic of Korea;
hamdy_kashtoh@ynu.ac.kr
* Correspondence: khbaek@ynu.ac.kr; Tel.: +82-53-810-3029

Abstract: The rising predominance of type 2 diabetes, combined with the poor medical effects seen with commercially available anti-diabetic medications, has motivated the development of innovative treatment approaches for regulating postprandial glucose levels. Natural carbohydrate digestion enzyme inhibitors might be a viable option for blocking dietary carbohydrate absorption with fewer side effects than manufactured medicines. Alpha-amylase is a metalloenzyme that facilitates digestion by breaking down polysaccharides into smaller molecules such as maltose and maltotriose. It also contributes to elevated blood glucose levels and postprandial hyperglycemia. As a result, scientists are being urged to target α-amylase and create inhibitors that can slow down the release of glucose from carbohydrate chains and prolong its absorption, thereby resulting in lower postprandial plasma glucose levels. Natural α-amylase inhibitors derived from plants have gained popularity as safe and cost-effective alternatives. The bioactive components responsible for the inhibitory actions of various plant extracts have been identified through phytochemical research, paving the way for further development and application. The majority of the findings, however, are based on in vitro investigations. Only a few animal experiments and very few human investigations have confirmed these findings. Despite some promising results, additional investigation is needed to develop feasible anti-diabetic drugs based on plant-derived pancreatic α-amylase inhibitors. This review summarizes the most recent findings from research on plant-derived pancreatic α-amylase inhibitors, including plant extracts and plant-derived bioactive compounds. Furthermore, it offers insights into the structural aspects of the crucial therapeutic target, α-amylases, in addition to their interactions with inhibitors.

Keywords: alpha-amylase; anti-diabetic activity; postprandial hyperglycemia; extract; natural compounds; type 2 diabetes

1. Introduction

Diabetes mellitus is a group of metabolic disorders marked by persistent increases in blood glucose levels. This condition is caused by a defect in insulin production, insulin function, or both factors. Insulin insufficiency and its resistance to the intended target tissues cause abnormalities in the metabolic processing of carbohydrates, lipids, and proteins [1–3]. Diabetes is linked to several short- and long-term health ramifications. Acute health problems include diabetic ketoacidosis, malignant hyperthermia-like syndrome with rhabdomyolysis, and hyperosmolar hyperglycemia, all of which carry a significant risk of morbidity and fatality in the near term [4,5]. The long-term ramifications might entail hypertension, lipid disorders, retinopathy, renal malfunction, nonalcoholic fatty liver disease, neurological diseases, cardiovascular and atherosclerotic problems, and others [4,5]. The most prevalent signs of hyperglycemia include polyuria, excessive thirst, unexplained weight loss, hyperphagia, and a lack of visual acuity [6]. Depending on the mode of its manifestation, there are several different types of diabetes, which include: (1) type 1 diabetes (T1D), which is caused by the destruction of pancreatic β-cells by the body's immune

system; (2) type 2 diabetes (T2D), which is characterized primarily by reduced insulin receptor sensitivity; (3) gestational diabetes (GD), which is recognized in the second or third trimester of pregnancy but was not concisely identified as diabetes prior to gestation; and (4) particular kinds of diabetes caused by different factors [7]. Diabetes mellitus is a major global disease, affecting over half a billion individuals in 2021, and the number of adults affected is expected to reach nearly 800 million by 2045 [8,9]. T2D, which is the most prevalent type (~90%), is a metabolic disorder that involves carbohydrate, lipid, and protein metabolic abnormalities as well as deficiencies in insulin secretion, typically accompanied by insulin resistance [10]. These chronic metabolic disorders may result in neuropathy, retinopathy, angiopathy, and nephropathy [11]. In this perspective, carbohydrate-digesting enzyme inhibition is regarded as a therapeutic strategy for the management and treatment of T2D. The most abundant carbohydrate in meals is starch, which is composed of two distinguished polysaccharides: one is linear with α-(1→4) glycosidic bonds (amylose), and the other is branched with α-(1→6) glycosidic bonds (amylopectin) [12]. Pancreatic α-amylase (EC 3.2.1.1) is the most essential digestive enzyme. It is a calcium-based metal-loenzyme that acts as a catalyst and facilitates the hydrolysis of the α-1,4 glycosidic bonds of polysaccharide molecules such as amylose, amylopectin, glycogen, and other maltodextrins and is accountable for the majority of starch digestion in humans. Another digestive enzyme, α-glucosidase or maltase (EC 3.2.1.20), catalyzes the final phase of carbohydrate digestion, acting on 1,4-alpha bonds to generate glucose (Figure 1) [13].
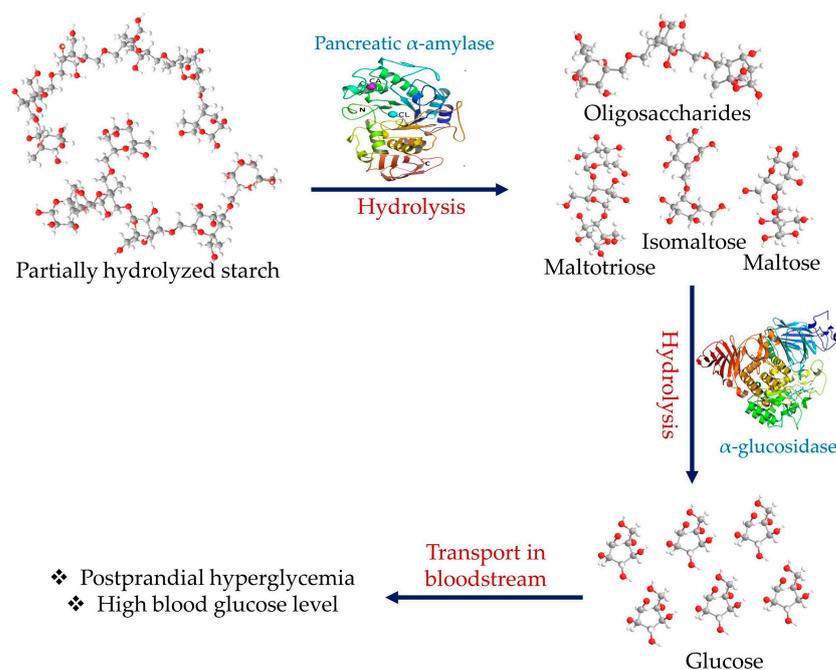

Figure 1. Schematic depiction of the involvement of α-amylase in postprandial hyperglycemia linked with starch hydrolysis.

Scientific investigations have shown the association between the activities of human pancreatic α-amylase (HPA) and postprandial glucose levels, highlighting the importance of lowering postprandial hyperglycemia (PPHG) in the management of T2D [14]. The capacity of α-amylase enzyme inhibitors to prevent the digestion and absorption of dietary starch has led to their being categorized as starch blockers. Nevertheless, α-pancreatic amylase activity inhibition should be moderated to avoid bacterial fermentation of non-digested carbohydrates in the colon caused by excessive suppression of the activity of this enzyme, which gives rise to diarrhea and flatulence [15]. There are already certain diabetes medications that work primarily by limiting carbohydrate digestion and absorption. The first α-glucosidase inhibitor accessible for diabetic therapy was acarbose, a microbial

inhibitor that inhibits α-amylase, maltase, and sucrase (EC 3.2.1.48) activities. Voglibose is a novel bacterial α-glucosidase inhibitor that suppresses maltase, isomaltase (EC 3.2.1.10), and sucrase activities, whereas miglitol is a 1-deoxynojirimycin derivative that functions by inhibiting the activities of glucoamylase (EC 3.2.1.3), sucrase, and isomaltase [16,17]. Although these medicines are effective in stabilizing postprandial blood glucose levels in a large number of individuals, they are frequently linked with substantial gastrointestinal side effects [16]. Furthermore, the undesirable clinical outcomes associated with marketed anti-hyperglycemic drugs are partly to blame for the common medication failure to comply that occurs in diabetes patients [18]. Because of the significant side effects of such medications, researchers have been looking for substitute therapies with minimal or no harmful effects. Although these anti-diabetic medicines are commercially available, several attempts have been made to produce non-cytotoxic anti-diabetic synthetic molecules [19–21]. From such a perspective, herbal chemicals intend to offer milder techniques of controlling metabolic problems and have been employed in traditional medical systems such as Indian Ayurveda (alternative medicine), Chinese herbal medicines, and Arabic Unani (traditional medicine used by the Muslims) since ancient times [22]. As a result, there is evidence suggesting the potentially helpful impact of a vast variety of medicinal herbs in T2D management [23]. Aside from their efficiency, herbal therapies appear to have few side effects and offer a cost-effective alternative to ingested commercial hypoglycemic medications. The World Health Organization (WHO) suggested in 1990 that extensive studies be conducted on the positive benefits of these plants [24]. In this regard, the current review highlights research on the α-amylase inhibitory action of plants and their phytochemical components, which may be effective in the treatment of diabetes. The review was conducted utilizing a scientific database composed of web search engines, including SciFinder, Scopus, Google Scholar, PubMed, and Science Direct, to examine published material between 2019 and 2023. Search criteria included 'amylase inhibitor', 'anti-diabetic characteristics', 'plant extracts', and 'pancreatic amylase'. The latest articles related to pancreatic amylase (porcine and human) inhibition by plant extracts were also included. Medical plants having a folkloric background and α-amylase activity met the inclusion requirements.

2. Alpha-Amylase Structure and Mechanism of Action

In the human diet, starch serves as the main energy source. Dietary sugars and starch are broken down to glucose by α-glucosidase and α-amylase enzymes. α-amylase metalloenzymes can be found in the saliva and pancreatic juice and are members of the glycoside hydrolase family 13 (GH13) [25–28]. Metalloenzymes are a diverse collection of enzymes that utilize a metal cation as a co-factor in the enzyme's active site. These enzymes stimulate a wide range of reactions, including hydrolytic activities [29]. α-amylase is a metalloenzyme that needs an important calcium ion for structural integrity and is activated by chloride ions [30–32]. Although this family's overall amino acid sequence homology is low, it has short regions of highly conserved residues, and structural investigations have shown that its members do have comparable three-dimensional structures [33]. These isozymes are members of a multigene family located on chromosome 1 that is controlled such that the various isozymes are only expressed in the pancreas or salivary glands [34]. The genes AMY1 and AMY2 produce both salivary and pancreatic α-amylase isozymes, each of which has 496 amino acids in one polypeptide chain [35–37]. Before starch is absorbed, salivary and pancreatic α-amylases hydrolyze it in the mouth and small intestine [25,38,39]. Through the cleavage of 1-4-α-glycosidic bonds, these isozymes hydrolyze carbohydrate polymers into shorter oligomers, such as maltose, a-limit dextrins, and maltotriose. An early partial cleavage into smaller oligomers (10–30%) is provided by the salivary isozyme [37,40]. When partially digested saccharides enter the gut, pancreatic amylase, which is produced in the pancreas and secreted into the lumen, extensively hydrolyzes them into smaller oligosaccharides [38]. Subsequently, α-glucosidases located in the brush border hydrolyze the α-amylase products further into glucose in the lumen of

the small intestine [25,39,41,42]. Afterward, glucose transporters take the glucose from the intestinal mucosa and transport it into the blood circulation [42].

The 3D structures of the α-amylase enzymes from human saliva, pancreas, and pig pancreas have been determined using X-ray crystallography [33,43,44]. These enzymes' architectures are all quite similar to one another. Three structural domains (A, B, and C) make up mammalian amylases, the biggest of which, Domain A, creates a standard core of (β-α)$_8$ barrel fold (Figure 2a), one end of which is positioned at the crucial active site residues (the catalytic triad of two aspartate (D197 and D300) and one glutamate (E233) residue) (Figure 3b). The active site is located in a substantial cleft that separates the carboxyl termini of the A and B domains. A bound chloride ion is present in Domain A as well, and it has been long recognized to activate amylase [32,45]. The bound chloride ion was found to form ligand interactions with R195, N298, and R337 in close proximity to the active site (Figure 2c) [33]. Domain B, the smallest domain, creates a calcium-binding site against Domain A's β-barrels. The bound Ca^{2+} ion in Domain B, which also borders the area of the active site, is likely crucial in preserving the active site region protein configuration. N100, R158, D167, and H201, which make ligand interactions with calcium, may greatly contribute to its function (Figure 2b). Anti-parallel β-structure makes up Domain C, which is only tangentially related to Domains A and B. Notably, a stable pyrrolidone derivative is created by post-translational alteration of human pancreatic a-amylase's N-terminal glutamate residue, which may offer defense against other digesting enzymes. It does not seem plausible that the molecule's N-terminal Domain C will directly contribute to the catalytic process as it has a weaker connection to Domains A and B [33,46].
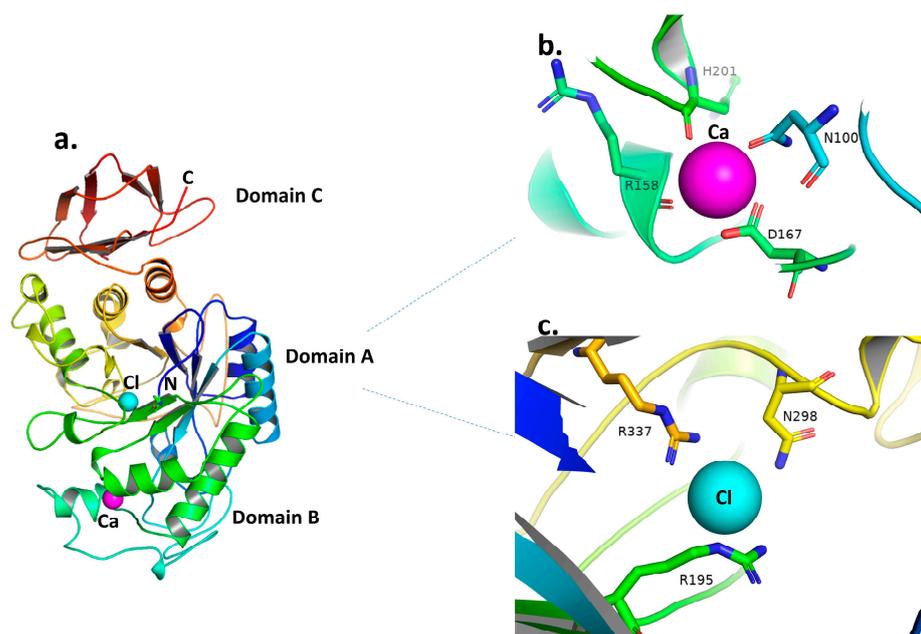

Figure 2. (**a**) Ribbon diagram of the structure of human pancreatic α-amylase as a representative for GH13 α-amylase. The three structural domains (A, B, and C) are indicated and colored as follows: Domain A in blues, greens, yellows, and oranges; Domain B in lime green and pale cyan; and Domain C in red. The N and C terminals are colored blue and red, respectively. The calcium and chloride ions are shown as magenta and cyan spheres, respectively. (**b**) Human pancreatic α-amylase calcium binding site; the sticks represent residues making ligand interactions with calcium, which is represented as a magenta sphere. (**c**) Human pancreatic α-amylase chloride binding site; the sticks represent residues making ligand interactions with chloride, which is represented as a cyan sphere. From the structure, (**a–c**) were adopted with PDB entry code 1HNY [33] and produced using PyMol [47].
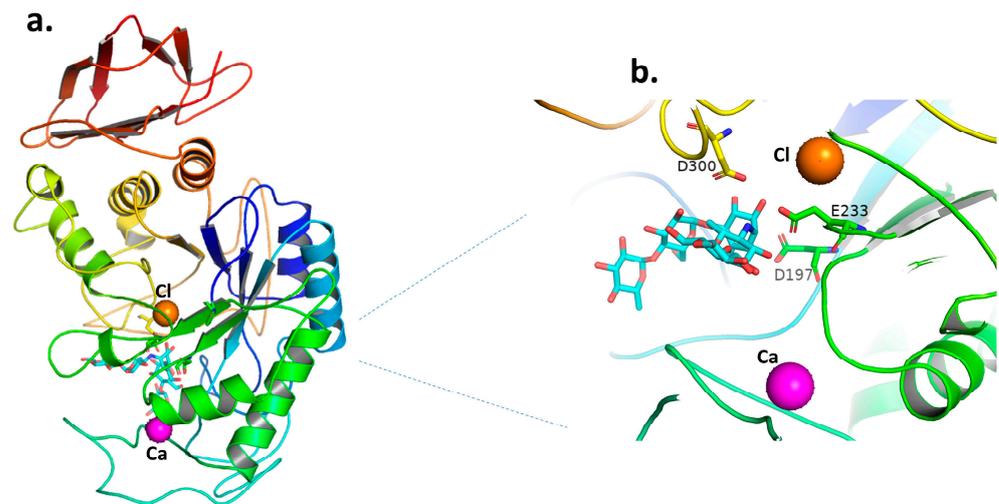
Figure 3. (**a**) The structure of the human pancreatic α-amylase/acarbose complex is depicted as a ribbon diagram. The chloride and calcium ions are represented as orange and magenta spheres, respectively, in (**a**,**b**). (**b**) The active site of the human pancreatic α-amylase/acarbose complex; residues located within a 4-A° radius of acarbose are represented as sticks (the catalytic triad of D197-D300-E233). The acarbose, shown as sticks in (**a**,**b**), is colored cyan. From the structure, (**a**,**b**) were adopted with PDB entry code 1B2Y [48] and produced using PyMol [47].

The catalytic processes in amylases are excellent representatives of a twofold displacement mechanism, in which the carboxyl groups of Asp and Glu residues serve as acid-base catalysts and a nucleophilic reactant in the creation of a covalent intermediate during the catalysis sequence. Through the use of a charge relay mechanism, a Cl^- ion may facilitate the protonation of a catalytically significant carboxyl group, leading to the activation [49–51]. With maltotriose and maltose as the main short oligomer yields (very little production of glucose), α-amylase is an endoenzyme that attacks linear sections of amylose and amylopectin several times [52–54]. According to kinetic studies, the pig pancreatic enzyme's active site may take up to five glucose molecules, meaning that there are five sub-sites where glucose molecules can bind [52]. Several three-dimensional structures demonstrated the presence of multiple sites, but the pig pancreatic amylase structure complexed with acarbose showed a sixth site [44]. The target of anti-diabetic drugs such as α-amylase and α-glucosidase inhibitors is to reduce postprandial hyperglycemia, with the most widely used ones being acarbose, voglibose, and miglitol. However, when used in therapy, the inhibitors of α-glucosidase and α-amylase have been associated with gastrointestinal adverse effects such as diarrhea, bloating, and flatulence. The quest for the development of novel α-amylase and α-glucosidase inhibitors is therefore crucial for the management of PPHG in T2D. Such insights into α-amylase's structure can be used to better understand the interaction of α-amylase with various inhibitors in order to develop anti-diabetic medicines with fewer adverse effects.

3. Plant Extracts as an α-Amylase Inhibitor Source

Several traditional medicines, in addition to the existing therapeutic options, have been promoted for diabetes therapy. Traditional plant medicines are used to manage a broad variety of diabetic symptoms all around the world. It is well acknowledged that plant remedies have fewer negative effects than modern pharmaceuticals [55–60], as well as being less expensive, driving both the public and healthcare institutions to investigate natural medicinal goods as alternatives to synthetic medications. As a consequence, studies on traditional medicinal herb-derived substances have grown in importance [61,62]. Several folkloric/medicinal plant extracts have been shown to possess potent α-amylase inhibition activity; however, further animal studies are needed to confirm their hypoglycemic physiological impact. Many studies investigated the potential role of medicinal plants in

inhibiting α-amylase enzymes (Table 1). Among the latest plant extracts investigated in the literature that are featured in this study, *Prosopis cineraria* (L.), *Terfezia claveryi*, *Chenopodium album* L., and *Salvia lavandulifolia Vahl* have the highest potential to inhibit α-amylase enzymes (Table 1).

Table 1. In Vitro α-amylase inhibition properties reported from various plant extracts.

Name of Plants	Used Extract/Fraction/Parts	IC$_{50}$	IC$_{50}$ (Control) (Acarbose)	Ref.
Argania spinosa	Roasted seeds oil	2.17 ± 0.24 mg/mL	0.41 ± 0.015 mg/mL	[63]
	Unroasted seeds oil	0.78 ± 0.16 mg/mL		
Melicope glabra (Blume) T. G. Hartley	Chloroform extracts (leaves)	303.64 ± 10.10 µg/mL	188.6 ± 14.31 µg/mL	[64]
Aloe megalacantha Baker	Leaf latex	74.76 ± 1.98 µg/mL	16.49 ± 1.91 µg/mL	[65]
Aloe monticola Reynolds		78.10 ± 1.88 µg/mL	16.49 ± 1.91 µg/mL	
Hedychium coronarium Koen	Ethyl acetate fraction (rhizomes)	58.15 ± 1.23 µg/mL	-	[66]
Cichorium endivia	Hydrophilic fraction (extracted from leaves with ethanol/water)	9.96 µg/mL	10.00 µg/mL	[67]
Brown rice	Brown rice (BR) extract	48.96 ± 0.34%	54.14 ± 0.35%	[68]
	BR/Vanillin	99.32 ± 1.18%	86.48 ± 0.71%	
	BR/Vanillyl alcohol	96.55 ± 0.12%		
Biyun no.7 (Kidney bean)	Aqueous extract	1.659 ± 0.050 U/g DW	-	[69]
Rhus coriaria L.	Ethyl acetate sub-extract (leaves)	20.810 ± 0.747 µg/mL	26.993 ± 0.797 µg/mL	[70]
Melicope latifolia	Chloroform extract (bark)	1464.32 µg/mL		[71]
Arachis hypogaea	Ethanol extract (peanut seeds)	0.61 µg/mL	0.32 µg/mL	[72]
Backhousia citriodora	Essential oil	0.49 mg/µL		[73]
Rosmarinus officinalis	Essential oil of rosemary plus	0.45 mg/µL		
Mentha piperita	Essential oil (leaf)	0.41 mg/µL	-	
Origanum vulgare	Essential oil (leaf-phenol type)	0.41 mg/µL		
Quercus variabilis Blume	Free polyphenol extract	5.25 ± 0.57 mg/mL	0.24 mg/mL	[74]
	Bound polyphenol extract	1.37 ± 0.11 mg/mL		
Centaurea pterocaula Trautv	Essential oil (aerial part)	79.66 ± 0.43 µg/mL	11.6 ± 0.18 µg/mL	[75]
Anchusa officinalis	Crude extract	954.16 ± 7.46 µg/mL	17.68 ± 1.24 µg/mL	[76]
Melilotus officinalis	Crude extract	1.32 ± 0.08 µg/mL		
Clausena indica	Hexane extract	1.37 ± 0.01 mg/mL	0.07 ± 0.00 mg/mL	[77]
	Ethyl acetate extract	8.56 ± 0.24 mg/mL		
Prosopis cineraria (L.)	n-Butanol fraction (pods)	22.01 ± 0.92 µg/mL	39.26 ± 2.19 µg/mL	[78]
	Ethyl acetate fraction	28.23 ± 1.06 µg/mL		

Table 1. *Cont.*

Name of Plants	Used Extract/Fraction/Parts	IC$_{50}$	IC$_{50}$ (Control) (Acarbose)	Ref.
Senna auriculata (L.) Roxb.	Methanolic extract (leaves)	49.45 µg/mL	-	[79]
Terfezia claveryi	Methanol extract	38.7 µg/mL	45.3 µg/mL	[80]
Rhododendron arboreum Sm.	Methanol extract	51.1%	-	[81]
Phragmites karka (Retz.)	Dichloromethane fraction (aerial part)	2.05 mg/mL	-	[82]
	n-Hexane fraction (aerial part)	2.08 mg/mL	-	
Morus nigra	Hexane fraction (leaves)	13.05 mg/mL	0 0.21 mg/mL	[83]
Salaria basilisca	Protein hydrolysates (peptide fraction F1)	71 µg/mL	14 µg/mL	[84]
Leucaena leucocephala (Lam.) De Wit	Ethanol extract (leaves)	288.01 µg/mL	252.59 µg/mL	[85]
Bergenia pacumbis	Methanol extract	14.03 ± 0.04 µg/mL	20.12 ± 0.12 µg/mL	[86]
Nonea obtusifolia (Wild.) DC.	Acetone extract	25.7 ± 0.08 µg/mL	28.18 ± 1.22 µg/mL	[87]
Morus alba Linn	Leaves	74.76 ± 6.76 µg/mL	35.34 ± 4.87 µg/mL	[88]
Phylanthus emblica L.	Methanolic extract (leaves)	98.37 ± 1.09%		[89]
Catunaregam spinosa	Dichloromethane fraction (bark)	77.17 ± 1.75 µg/mL	6.34 ± 0.07 µg/mL	[90]
Chenopodium album L.	Flavonoid fraction (aerial part)	122.18 ± 1.15 µg/mL	812.83 ± 1.07 µg/mL	[91]
Solanum virginianum	Aqueous extract (fruits)	54.12 ± 0.44–86.80 ± 0.27%	58.36 ± 0.30–88.24 ± 0.16%	[92]
	Ethanolic extract (fruits)	23.07 ± 0.47–81.61 ± 0.43%		
Eucalyptus globulus	Ethanol extract (Hexane defatted)	23.6 ± 1.2 µg/mL	5.2 ± 1.3 µg/mL	[93]
	Ethanol extract (non-defatted)	14.8 ± 1.2 µg/mL		
Maesobotrya dusenii Hutch.	Crude methanol extract	24 µg/mL	28 µg/mL	[94]
Veronica biloba	Aqueous extract	110.25 µg/mL	138.79 µg/mL	[95]
	Ethyl acetate extract	121.09 µg/mL		
	Dichloromethane extract	123.68 µg/mL		
Salvia lavandulifolia Vahl	Aqueous extract	0.99 ± 0.00 mg/mL	0.52 ± 0.01 mg/mL	[96]
Moringa oleifera	Methanolic crude extract (leaves)	65.6 ± 4.93%	-	[97]
Ziziphus mucronata	Acetone extract	0.62 mg/mL	0.42 mg/mL	[98]
Englerophytum magalismontanum	Methanol fraction (leaves)	10.76 ± 1.33 µg/mL	1.24 ± 1.64 µg/mL	[99]

Table 1. *Cont.*

Name of Plants	Used Extract/Fraction/Parts	IC$_{50}$	IC$_{50}$ (Control) (Acarbose)	Ref.
Achyranthes aspera	Crude extract	97.60 ± 1.11 µg/mL	68.13 ± 0.46 µg/mL	[100]
Catharanthus roseus		94.05 ± 1.18 µg/mL		
Pterocarpus marsupium	Methanolic extract	158.663 ± 10.986 µg/mL	56.060 ± 4.465 µg/mL	[101]
Rubus corchorifolius L.	70% ethanolic extract (leaf tea)	1.26 ± 0.03 mg/mL	5.12 ± 0.42 mg/mL	[102]
	70% methanolic extract (leaf tea)	1.47 ± 0.05 mg/mL		
	Aqueous extract (leaf tea)	4.39 ± 0.17 mg/mL		
Sterculia nobilis Smith	Ethyl acetate fraction (pericarp)	13.550 ± 0.230 µg/mL	19.45 ± 0.26 µg/mL	[103]

A recent study investigated the hypoglycemic effect of edible plant leaves from Palestine that are used as folkloric anti-diabetic remedies [67]. The lipophilic and hydrophobic fractions of these plants were tested against the porcine pancreatic α-amylase enzyme. The hydrophilic fractions of *Centaurea iberica* and *Cichorium endivia* showed the highest α-amylase activity with IC$_{50}$ values of 12.33 µg/mL and 9.96 µg/mL, respectively. Furthermore, the highest α-amylase inhibition effect for lipophilic fractions was observed for *Sisymbrium irio* and *Arum palaestinum*, with IC$_{50}$ values of 7.72 µg/mL and 25.3 µg/mL, respectively. Additionally, rice extract's biological activity against α-amylase was investigated in Thailand, and the study showed that brown rice extract as well as the rice's volatile compounds, identified as vanillin and vanillyl alcohol, have high inhibitory effects against α-amylase [68]. It is notable to mention that a synergy effect was noticed on α-amylase inhibition activity when a combination of black, red, and white rice extracts along with vanillin and vanillyl alcohol was used.

Rhus coriaria L. leaves and fruits are an important folk medicine that is used in Turkey for the treatment of diabetes [104]. Gök et al. studied the effect of *R. coriaria* ethanol extracts of leaf and fruit on α-amylase inhibitory activity in an attempt to isolate the active compounds against α-amylase [70]. The ethyl sub-extract of *R. coriaria* showed good α-amylase inhibition activity with an IC$_{50}$ of 20.81 µg/mL against 26.99 µg/mL for acarbose. The study showed the successful isolation of several compounds; among them, penta-*O*-galloyl-β-glucopyranose, one of the main compounds in leaf and fruit extracts, had α-amylase inhibition activity with an IC$_{50}$ of 6.32 µM compared to 10.69 µM for acarbose. Peanuts (*Arachis hypogaea*), another edible food, were investigated for their α-amylase inhibition property [72]. Various organic extracts of peanuts were investigated, and it was found that peanut seed ethanol extract has an α-amylase suppressing ability with an IC$_{50}$ of 0.61 µg/mL, close to 0.31 µg/mL for acarbose, and the least cytotoxicity with an LC$_{50}$ of 413.9 µg/mL. *Melilotus officinalis* (yellow sweet clover) is a medicinal plant typically employed in Asia and Europe and has been used as an anti-inflammatory traditional medicine [105,106]. As *M. officinalis* contains a high amount of coumarin derivatives, its extracts were clinically tested for the treatment of diabetic foot [107]. Paun et al. studied the polyphenolic-rich extracts of *M. officinalis* and their anti-diabetic activity [76]. *M. officinalis* polyphenolic-rich extracts displayed notable α-amylase inhibitory activity with an IC$_{50}$ of 1.30 µg/mL, while acarbose showed an IC$_{50}$ of 17.68 µg/mL, suggesting that it could be a good candidate for developing a natural anti-diabetic food supplement.

Solanum species are a rich source of traditional medicine remedies as antipyretic, anti-inflammatory, antioxidant, and anti-diabetic agents [108–110]. Ju'a-açu fruit (*Solanum oocarpum*), also known as Brazilian sunberry, has an alkaloid composition and has been reported to have anti-diabetic activity [111]. Saraswathi et al. studied the phytoconstituents

of the ethanolic and aqueous extracts of *Solanum virginianum* dried fruits for their anti-diabetic activity [92]. The study showed that both the ethanolic and aqueous fruit extracts have α-amylase inhibition activity, with the aqueous extract having higher enzymatic inhibition activity (54.12–86.80%) than the ethanolic extract (23.07–81.61%).

In China, raspberry leaves are consumed as tea, and it has been reported to have anti-diabetic activity [112]. In a recent study, Li et al. investigated the inhibitory activity of raspberry leaf tea (*Rubus corchorifolius* L.) (RLT) extract digestive enzymes and found potent α-amylase inhibition activity for its ethanolic, methanolic, and aqueous extracts with an IC_{50} of 1.26 mg/mL, 1.47 mg/mL, and 4.39 mg/mL, respectively, against an IC_{50} of 5.12 mg/mL for acarbose aqueous extract [102]. The study identified the major inhibitors responsible for the extract activity as epigallocatechin gallate (EGCG), isovitexin, rutin, isoorientin, procyanidin, delphinidin-3-*O*-glucoside, dihydromyricetin, and procyanidin C3. The authors conducted additional molecular docking analyses and discovered these inhibitors interact with the digestive enzyme through hydrogen bonds or van der Waals forces, resulting in the retardation of enzyme activity [102]. Mikailu et al. studied the effect of the stem bark *Maesobotrya dusenii* Hutch methanol extract on α-amylase inhibition activity. The authors found that all the extracts showed significant amylase activity with 56.7% inhibition in a dose-dependent manner. *Maesobotrya dusenii* Hutch crude methanol extract showed α-amylase activity with an IC_{50} of 24 μg/mL against 28 μg/mL for acarbose.

Sterculia nobilis Smith seeds, leaves, and nuts are used to prepare several food dishes in China. It is commonly native to Vietnam, Indonesia, Japan, and south China and is usually utilized to heal gastrointestinal and circulatory problems [113–115]. The dark red shell of *S. nobilis* Smith fruit (pericarp) has been investigated for its inhibition activity against digestive enzymes [103]. The study showed that the pericarp ethyl acetate fraction has a potent uncompetitive α-amylase activity, with an IC_{50} of 13.55 μg/mL against 19.45 μg/mL for acarbose. Spectroscopic methods were used to elaborate the mechanism of α-amylase inhibition, and the results showed the ethyl acetate fraction alters the enzyme's secondary structure and tryptophan/tyrosine residue microenvironment, resulting in enzyme activity inhibition [103]. The early investigation of these traditional medicinal plant extracts demonstrated promising α-amylase inhibitory activity, but more research is needed to confirm their anti-diabetic impact.

Prosopis cineraria (L.) Druce pods are usually used in diets as a vegetable in the Indian subcontinent and have been reported to have anti-diabetic properties [116]. Kumar et al. studied the anti-diabetic effect of *P. cineraria* pod extracts in vitro as well as in vivo (Table 2) [78]. The study shows that n-butanol fractions from the pods have potent α-amylase inhibition activity with an IC_{50} of 22.01 μg/mL against 39.26 μg/mL for acarbose. The n-butanol fraction was investigated for toxicity and found to be non-toxic when the mice ingested an oral dose of the fraction up to 2000 mg/kg. Further studies are required to investigate the *P. cineraria* pods as a promising anti-diabetic candidate. A recent study showed *Terfeziaclaveryi* (truffle, a fungus that grows wildly in the desert) methanol extract to have an α-amylase inhibition activity of 38.7 μg/mL, which is higher when compared to 45.3 μg/mL of acarbose [80]. The in vivo anti-diabetic activity showed that a 200 mg/kg dose of *Terfeziaclaveryi* methanol extract reduced the fasting plasma glucose level. *Chenopodium album* L. is another anti-diabetic herbal remedy candidate that showed promising α-amylase activity from its methanolic and aqueous root extracts [117,118]. *C. album* aerial parts' alkaloid fraction (CAAF) showed a more potent α-amylase enzyme inhibition activity than acarbose, with an IC_{50} of 122.18 μg/mL and 812.83 μg/mL, respectively [91]. The CAAF fraction did not produce severe toxicity in vivo and showed promising anti-diabetic activity in a dose-dependent manner. The study suggests that the CAAF acts primarily as an α-amylase inhibitor. *Salvia lavandulifolia* Vahl is commonly found in the Mediterranean basin, and as a traditional medicine, it is applied as a virucidal, fungicidal, and bactericidal agent [119,120]. Its aqueous extract is widely used in this region as an anti-diabetic remedy for its hypoglycemic effect [121]. Remo et al. investigated the aqueous extract of *S. lavandulifolia* Vahl for its α-amylase inhibitory

activity as well as its hypoglycemic effect in vivo [96]. The aqueous extract showed significant α-amylase inhibition activity with an IC_{50} of 0.99 mg/mL compared to an IC_{50} of 0.52 mg/mL for acarbose. It also showed a hypoglycemic effect on diabetic rats, with an AUC of 51.94 g/L/h. This study shows that *S. lavandulifolia* is a potential candidate for anti-diabetic drugs (Table 2).

Table 2. List of in vivo effects of α-amylase inhibitors reported from several plant extracts.

Plant Extracts	Dosage of Plant Extract Used	Experimental Animals	Types of Diabetes Induction	Administration Route	Diagnostic Criteria	Inference	Ref.
Oxalis pes-caprae Methanolic extract	150 mg/kg BW	Swiss albino mice	Alloxan-induced diabetes	Intraperitoneal injection	Fasting blood glucose (FBG) level, body weight	Hypoglycemic	[122]
Cardamine hirsuta Linn Hydro-methanolic extract	125, 250, and 500 mg/kg BW	Male Sprague Dawley (SD) rats	High-fat diet (HFD), Streptozotocin (STZ)-induced diabetes	Oral and intraperitoneal injection	FBG level	Hypoglycemic, dose-dependent	[123]
Trachinotus ovatus Protein hydrolysates	100, 500, and 1000 mg/kg BW	Male Kunming mice	STZ-induced diabetes	Intraperitoneal injection	FBG level	Hypoglycemic, dose-dependent	[124]
Sorbaria tomentosa Lindl. Rehder Methanolic extract	150 and 300 mg/kg BW	Rats	Alloxan-induced diabetes	Intraperitoneal injection	FBG level	Hypoglycemic	[125]
Chenopodium album L. Flavonoid fraction	500 mg/kg BW	SD rats	HFD-STZ-induced diabetes	Oral and intraperitoneal injection	Glucose, cholesterol, and triglyceride levels	Hypoglycemic	[91]
Terfezia claveryi Methanolic extract	200 mg/kg BW	Male Wistar albino rats	STZ-induced diabetes	Intraperitoneal injection	FBG level	Hypoglycemic time-dependent	[80]
Salvia lavandulifolia Vahl Aqueous extract	400 mg/kg BW	Normal rats	D-glucose, 2 g/kg	Oral	Oral glucose tolerance test (OGTT) Blood glucose level	Hypoglycemic	[96]
Artemisia absinthium L. Aqueous extract	200 mg/kg BW	Wistar rats	Alloxan-induced diabetes	Oral	Postprandial blood glucose (PBG) level	Hypoglycemic	[126]
Ammodaucus leucotrichus Coss. and Durieu Aqueous extract	150 mg/kg BW	Wistar albino rats	Alloxan-induced diabetes	Oral	OGTT	Hypoglycemic	[127]

Table 2. *Cont.*

Plant Extracts	Dosage of Plant Extract Used	Experimental Animals	Types of Diabetes Induction	Administration Route	Diagnostic Criteria	Inference	Ref.
Porphyra spp. Polysaccharides	100 mg/kg BW	Rats	-	Oral	PBG level	Hypoglycemic	[128]
Prosopis cineraria Ethyl acetate fraction/n-Butanol fraction	250, 500, 1000 and 2000 mg/kg BW	Swiss albino mice	Sucrose tolerance test (OSTT)	Oral	Serum glucose concentration	Hypoglycemic	[78]
Allium sativum L. Polysaccharides	1.25, 2.5, and 5 g/kg BW	Male Kunming mice	STZ-induced diabetes	Intraperitoneal injection	OGTT, FBG	Hypoglycemic	[129]

4. Secondary Metabolites Isolated from Various Plant Sources as Potential α-Amylase Inhibitors

Many different plant extracts have been used for therapeutic purposes throughout history, whether on purpose or by accident. There have been reports of numerous plant extracts and their secondary metabolites having anti-diabetic effects, particularly through α-amylase or α-glucosidase inhibition [130,131]. Due to their fewer adverse side effects and easy accessibility, there is a growing interest in developing medicinal plant extracts or the extracted secondary metabolites as an alternative and complementary natural therapeutic for the medical care of diabetes [132,133]. Several secondary metabolite groups, including flavonoids, polysaccharides, phenolic acids, terpenoids, tannins, alkaloids, and xanthones, have been identified as prospective inhibitors of the α-amylase enzyme (Figure 4, Table 3).
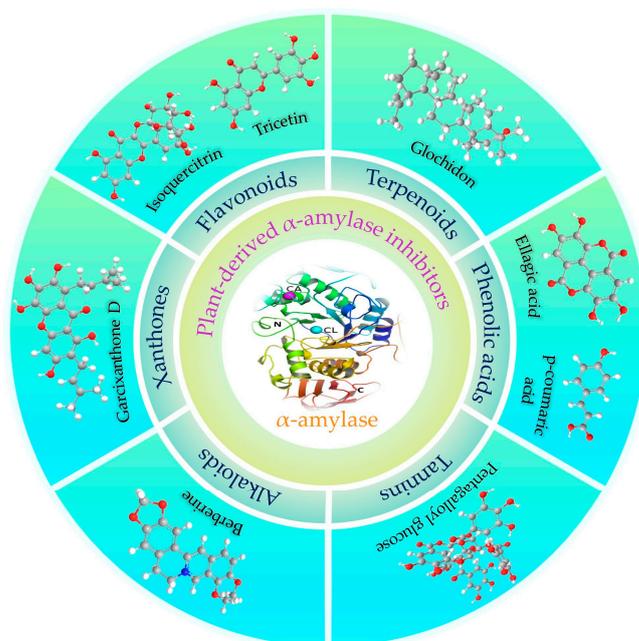

Figure 4. A diagram depicting the numerous plant-derived compounds that are effective α-amylase inhibitors.

Table 3. List of α-amylase inhibitors (in vitro) isolated from diverse plant species.

Class of Compounds	Bioactive Compound	Source (Plant's Name)	IC$_{50}$	IC$_{50}$ (Control) (Acarbose)	Ref.
Flavonoids	5-hydroxy-2-(4-methoxy-3-((E)-3-methylbut-1-enyl)-5-(3-methylbut-3-enyl)phenyl)chroman-4-one	*Andrographis echioides*	3.357 µg/mL		[134]
	Luteolin	*Taraxacum mongolicum*	42.33 ± 0.82 µg/mL	-	[135]
	Isoquercitrin	*Melilotus officinalis*	9.65 ± 0.43 µg/mL	17.68 ± 1.24 µg/mL	[76]
	Epicatechin gallate	*Euryale ferox* (seed coat)	0.92 mg/mL	1.08 mg/mL	[136]
	Puerarin	*Agave americana* L.	3.87 µM		[137]
Flavonoid glucoside	Tricetin	*Punica granatum*	0.43 ± 0.12 mg/mL	0.038 ± 0.017 mg/mL	[138]
	Tricetin 4′-*O*-β-glucopyranoside		1.17 ± 0.32 mg/mL		
	Rutin	*Melilotus officinalis*	11.42 ± 0.62 µg/mL	17.68 ± 1.24 µg/mL	[76]
	quercetagetin-7-*O*-β-D-glucopyranoside	*Tagetes minuta* L.	7.8 µM	7.1 µM	[139]
	luteolin-7-*O*-α-L-rhamnoside	*Phylanthus emblica* L.	89.79%	-	[89]
	hypolaetin 8-*O*-β-D-galactopyranoside	*Thymelaea tartonraira* (leaves)	46.49 ± 2.32 µg/mL	0.44 ± 0.022 µg/mL	[140]
Ent-kaurane diterpenoids	Wedtriloside A	*Wedelia trilobata* (leaves)	112.20 ± 2.87 µg/mL	-	[141]
	Wedtriloside B		87.10 ± 1.89 µg/mL		
Abietane diterpene	Carnosol	*Salvia aurita* (aerial part)	19.8 ± 1.4 µg/mL	10.2 ± 0.6 µg/mL	[142]
	12-methoxycarnosic acid		16.2 ± 0.3 µg/mL		
Pentacyclic triterpenoid	Oleanolic acid	*Xylopia aethiopica* (Dunal) A. Rich. (fruit)	89.02 ± 1.12 µM	-	[143]
Triterpenoid	Glochidon	*Phyllanthus debilis*	38.15 ± 1.40 µM	33.68 ± 3.12 µM	[144]
Triterpenoid saponin	Ligularoside A	*Passiflora ligularis* Juss (leaves)	409.8 ± 11.4 µM	234.1 ± 15.9 µM	[145]
Phenylpropanoids	Jionoside D	*Clerodendrum infortunatum* L.	3.4 ± 0.2 µM	5.9 ± 0.1 µM	[146]
Polysaccharides	WSRP-2a	*Rosa setate* × *Rosa rugosa* (waste biomass)	3.41 mg/mL	0.57 mg/mL	[147]
	WSRP-2b		1.72 mg/mL		
	PD-1	*Porphyra* spp.	12.72 mg/mL		[128]
	SGP-1-1	*Siraitia grosvenorii*	61.73% at 1 mg/mL		[148]
	LLP50 (polysaccharides fraction)	*Lycium barbarum* (leaves)	1.659 mg/mL	0.0002 mg/mL	[149]
	Xyloglucan	*Tamarindus indica* L	72.49 ± 0.84%	92.49 ± 1.97%	[150]

Table 3. *Cont.*

Class of Compounds	Bioactive Compound	Source (Plant's Name)	IC$_{50}$	IC$_{50}$ (Control) (Acarbose)	Ref.
Phenolic acid and its derivatives	Ellagic acid	*Quercus variabilis* Blume	0.19 ± 0.02 μg/mL	0.24 μg/mL	[74]
	Rosmaric acid	*Anchusa officinalis*	0.92 ± 0.07 μg/mL	17.68 ± 1.24 μg/mL	[76]
	Chlorogenic acid		1.84 ± 0.05 μg/mL		
	p-Coumaric acid	*Agave americana* L.	10.16 μM	-	[137]
Ellagitannins	Chingiitannin A	*Rubus chingii* Hu (unripe fruit/n-BuOH fraction)	4.52 ± 0.30 μM	35.71 ± 4.93 μM	[151]
	Lambertianin A		10.32 ± 0.10 μM		
	Sanguiin H-6		11.00 ± 0.21 μM		
Gallotanins	1,2,3,4,6-penta-*O*-galloyl-β-D-glucopyranose	*Rhus coriaria* (leaves)	6.32 ± 0.18 μM	10.69 ± 0.50 μM	[70]
Dihydrostilbene glycosides	Sasastilboside A	*Camellia sasanqua* Thunb (leaves)	53.7 ± 1.6 μM	-	[152]
Proanthocyanidins	Chinese bayberry leaves proanthocyanidins	*Myrica rubra* Sieb. et Zucc. (leaves)	3.075 ± 0.073 μg/mL	-	[153]
Phenolic	Dehydrodieugenol B	*Ocimum tenuiflorum*	29.6 μM	13.85 μM	[154]
Coumarin	Halfordin	*Melicope latifolia*	197.53 μM	282.39 ± 8.14 μM	[71]
Alkaloids	3,3′,5,5′,8-pentamethyl-3,3′-bis(4-methylpent-3-en-1-yl)-3,3′,11,11′-tetrahydro-10,10′-bipyrano[3,2-a]carbazole	*Murraya koenigii* (L.)	30.32 ± 0.34 ppm	-	[155]
	Berberine	*Cardiospermum halicacabum*	72% at 10 μg/mL		[156]
Pregnane glycosides	Drevoluoside Q	*Dregea volubilis* (leaves)	51.3 ± 2.1 μM	36.3 ± 0.5 μM	[157]
	Gymsyloside B	*Gymnema sylvestre* (leaves)	175.8 ± 2.3 μM	72.4 ± 0.8 μM	[158]
	Gymsyloside C		162.2 ± 2.7 μM		
	Gymsyloside D		113.0 ± 0.7 μM		
Prenylated xanthones	Mangoxanthone A	*Garcinia mangostana* (pericarp)	22.74 ± 2.07 μM	-	[159]
Xanthone	Garcixanthone D	*Garcinia mangostana* (pericarp)	93.8%	96.4%	[160]
	Garcinone E		85.6%		
Xanthophyll	Fucoxanthin	*Phaeodactylum tricornutum*	28.38 ± 0.67 mmol/L	25.01 ± 1.38 mmol/L	[161]
Fatty acid	5,7-dihydroxy-6-oxoheptadecanoic acid	*Tiliacora triandra*	26.27 ± 1.11 μM.	177.65 ± 0.88 μM	[162]
Phytosterols	β-Sitosterol	*Parthenium hysterophorus* (leaves)	42.30% (at 400 μg/mL)	-	[163]

4.1. Flavonoids

Flavonoids are the most ubiquitous class of secondary metabolites present in plants [164]. They are broadly studied due to their wide range of bioactivities, which include anti-

oxidant [77], anti-inflammatory [165], anti-microbial [166], and anti-diabetic properties [167]. Numerous groups of flavonoids have the potential to inhibit α-amylase enzymes due to their non-covalent binding ability to the active site residues of the enzyme [168].

A flavone derivative, 5-hydroxy-2-(4-methoxy-3-((E)-3-methylbut-1-enyl)-5-(3-methylbut-3-enyl)phenyl)chroman-4-one (Figure 5a), identified in *Andrographis echioides* leaf, was found to dramatically inhibit α-amylase (IC_{50} = 3.35 μg/mL) and enhance glucose intake in the 3T3-L1 and L6 cell lines [134]. Another study conducted by Zhang et al. [136] revealed that epicatechin gallate (Figure 5b) (IC_{50} = 0.92 mg/mL) isolated from *Euryale ferox* seed coat possessed good inhibitory effects against α-amylase in comparison to acarbose (IC_{50} = 1.08 mg/mL). Similarly, Wu and Tian [138] isolated a new flavone glycoside, tricetin 4′-*O*-β-glucopyranoside (Figure 5c), along with a known flavone, Tricetin (Figure 5d), from the flowers of *Punica granatum*. Tricetin 4′-*O*-β-glucopyranoside (IC_{50} = 1.17 mg/mL) and Tricetin (IC_{50} = 0.43 mg/mL) both exhibited α-amylase inhibitory activities comparable to acarbose (IC_{50} = 0.03mg/mL). In addition, a new α-glucosidase and α-amylase inhibitor flavonoid named hypolaetin 8-*O*-β-D-galactopyranoside (Figure 5e) was isolated from the leaves of *Thymelaea tartonraira* [140].
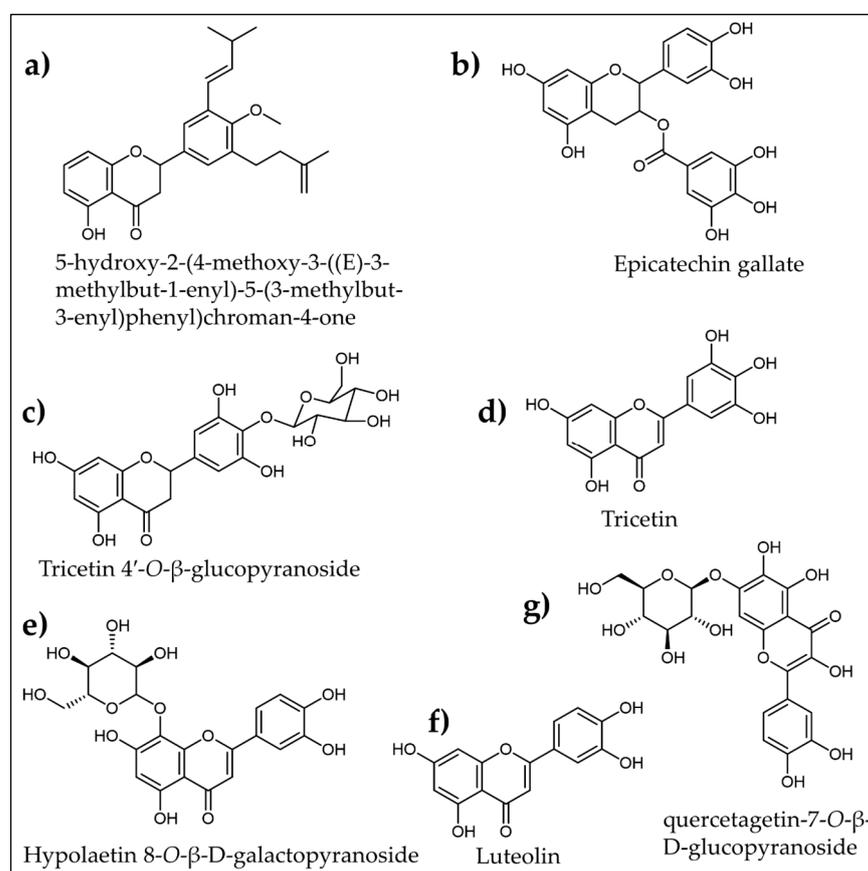

Figure 5. Molecular structures of various plant-derived flavonoids identified as α-amylase inhibitors.

Yang et al. [135] separated luteolin (Figure 5f) from *Taraxacum mongolicum*, which inhibits the α-amylase enzyme (IC_{50} = 42.33 μg/mL). From the molecular docking studies, they found that luteolin restricts the bioactivity of α-amylase by making a stable complex with the enzyme through Van der Waals forces, hydrogen bonding, and hydrophobic interaction. In a recent study, Mohamed and his co-workers [139] assessed 12 different flavonoids from *Tagetes minuta* for α-amylase inhibitory activities by in vitro experiments and in silico analyses. Compared to acarbose, quercetagetin-7-*O*-β-D-glucopyranoside (Figure 5g) showed the best in vitro enzyme inhibition (IC_{50} of 7.8 μM), more stability, and the highest binding affinity with the receptor in in silico studies. Such encouraging results

are prompting us to further explore the flavonoid molecules and their interaction with α-amylase enzymes in in vivo studies, toxicity assessments, and the development of new anti-diabetic therapeutics.

4.2. Terpenoids

Terpenoids are among the diverse classes of natural compounds with potent medicinal qualities such as anti-cancer, anti-inflammatory, and antiviral properties [169]. They are major constituents of essential oils produced by aromatic plants and contribute to their flavor and fragrance [170]. Medicinal plant-derived terpenoids have been found to have promising hypoglycemic effects [171].

As part of the search for new anti-diabetic compounds from plants, Luyen et al. [141] examined the Vietnamese medicinal plant *Wedelia trilobata*, which was well-known for its efficacy in treating type 2 diabetes. They discovered wedtrilosides A and B (Figure 6a,b), two new ent-kaurane diterpenoids that have α-amylase inhibition activities. Furthermore, abietane diterpenes, carnosol (Figure 6c) and 12-methoxycarnosic acid (Figure 6d), isolated from *Salvia aurita*, revealed strong α-amylase inhibition with an IC_{50} of 19.8 and 16.2 μg/mL, respectively [142]. Similarly, oleanolic acid (Figure 6e) from *Salvia Africana-lutea* exhibited an α-amylase inhibition property with an IC_{50} of 12.5 μg/mL, close to acarbose (IC_{50} = 10.2 μg/mL) [172]. Another new terpenoid saponin molecule, ligularoside A (Figure 6f), was reported for the first time from *Passiflora ligularis* Juss leaves and showed a comparable inhibitory effect over α-amylase with an IC_{50} of 409 μM in an in vitro assay against acarbose, which had an IC_{50} of 234 μM [145].
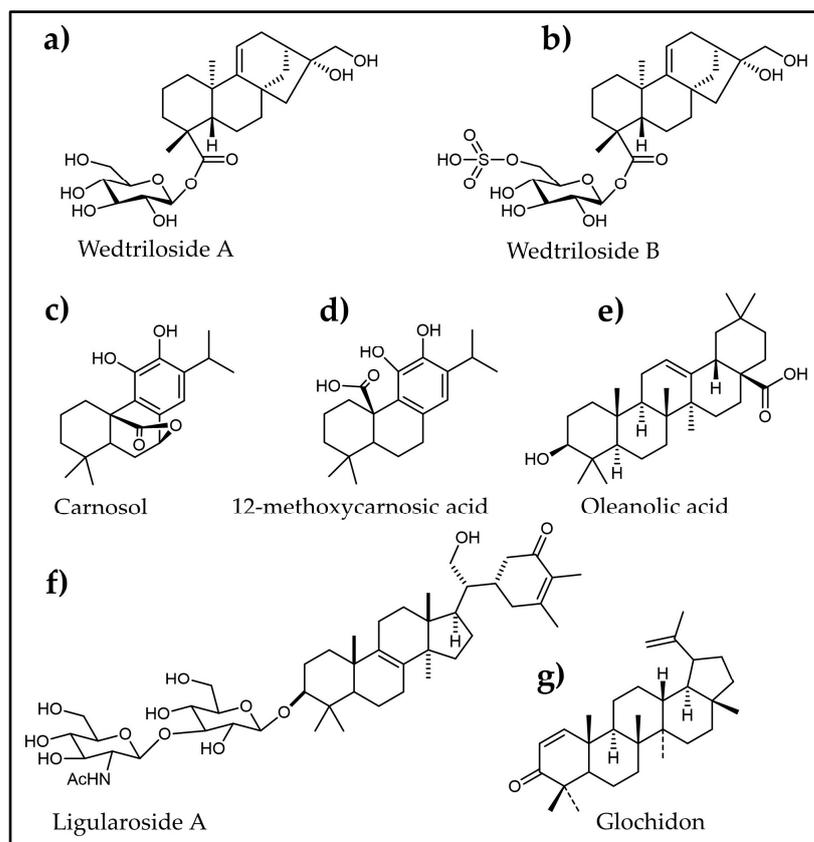

Figure 6. Molecular structures of various plant-derived terpenoids identified as α-amylase inhibitors.

Verma et al. [144] evaluated the anti-diabetic property of a novel triterpenoid, glochidon (Figure 6g), isolated from *Phyllanthus debilis* by in vitro assays, in vivo trials, and computational studies. In the in vitro assays, glochidon showed excellent α-amylase inhibition (IC_{50} = 38.15 μM), which is almost the same as that of acarbose. Additionally, it

showed dose-dependent hypoglycemic effects in STZ-induced diabetic rats. Furthermore, the molecular dynamic simulations demonstrated that glochidon has a higher propensity to interact with the GLUT1 receptor protein. These findings can be utilized in the development of terpenoid-based natural medicine for both the management and avoidance of diabetes and its intricacies.

4.3. Polysaccharides

Polysaccharides derived from plants are macromolecules that consist of the same or different monosaccharide units interconnected with α- or β-glycosidic linkages. They have lengthy chains composed of carbohydrate molecules arranged either linearly as in amylose and cellulose or branched as in amylopectin and glycogen [173,174]. The composition, structure, and molecular weight of the polysaccharides vary with the plant species. Polysaccharide composition, molecular weight, linkage types, and chain patterns all influence their physical properties, such as solubility and viscosity, as well as chemical properties affecting pharmacological effects [175,176]. Plant polysaccharides have received a lot of interest in recent years due to their noteworthy bioactivities, non-toxic nature, and suitability for use in medicine [177–179]. Recent studies showed that many plant polysaccharides inhibit the α-amylase enzyme and play a crucial role in the treatment of diabetes [180–182].

It has been identified that the polysaccharides from *Lycium barbarum* leaves hinder α-amylase enzyme activity in a dose-dependent manner [149]. Another polysaccharide (SGP-1-1), isolated from *Siraitia grosvenorii,* showed α-amylase inhibition with the best inhibition of 61.73% [148]. Similarly, Zeng et al. [128] exploited the red seaweed laver-derived polysaccharide as a hypoglycemic agent. The polysaccharide named PD-1 showed 98.78% inhibition effects on the α-amylase enzyme with an IC_{50} of 12.72 mg/mL. Furthermore, the kinetic studies reveal that PD-1 interacts with the α-amylase enzyme in a competitive manner. Another group of researchers purified two polysaccharides, WSRP-2a (MW 56.8 kD) and WSRP-2b (MW 23.9 kD), from *Rosa Setate x Rosa Rugosa* biomass waste. The inhibition of the α-amylase enzyme by WSRP-2b (IC_{50} = 1.72 mg/mL) was much stronger compared to WSRP-2a (IC_{50} = 3.41 mg/mL), which may be related to changes in molecular weight [147]. Jiang and his coworkers used the ultrasonic-assisted extraction method to extract tamarind (Xyloglucan). When compared to Xyloglucan extracted using the hot water approach, they discovered that the ultrasound-aided extraction method greatly improved its α-amylase inhibitory activity (72.49%) by successfully reducing the viscosity and molecular weight of the compound [150]. In light of these encouraging results, additional research and examinations are needed to determine the correlation between the molecular structure and the anti-diabetic properties of polysaccharides and to create anti-diabetic medications derived from plant polysaccharides.

4.4. Phenolic Acids

Phenolic acids are the derivates of cinnamic and benzoic acids and are found in wide varieties of plants, either in free or bound forms [183]. Phenolic acids have been known for diverse bioactivities, including anti-microbial, antioxidant, anti-diabetic, and anti-cancer activities [184]. In carbohydrate metabolism, phenolic acids have been best known for their ability to inhibit the bioactivity of the α-glucosidase and α-amylase enzymes [185].

Wu et al. [74] studied the α-amylase inhibitory effects of ellagic acid (Figure 7a) obtained from corn kernels, which showed better inhibition (IC_{50} = 0.19 mg/mL) than the control (IC_{50} = 0.24 mg/mL). Similarly, Paun et al. [76] isolated rosmarinic acid (Figure 7b) and chlorogenic acids (Figure 7c) from *Anchusa officinalis*. Among these phenolic acids, rosmarinic acid (IC_{50} = 0.92 μg/mL) showed almost 20 fold higher inhibitory effects on the α-amylase enzyme than the standard sample (IC_{50} = 17.68 μg/mL). Likewise, another phenolic acid, p-coumaric acid (Figure 7d), identified in *Agave americana* L., showed considerable inhibition of the human α-amylase enzyme with an IC_{50} of 10.16 μM, which was around 2.3 times higher than the control [137]. In addition, the kinetic studies revealed

that p-coumaric acid functions as a competitive α-amylase enzyme inhibitor. To fully realize the potential of phenolic acid compounds as a novel therapeutic for treating diabetes, more study is required to evaluate their efficacy, bioavailability, and safety.
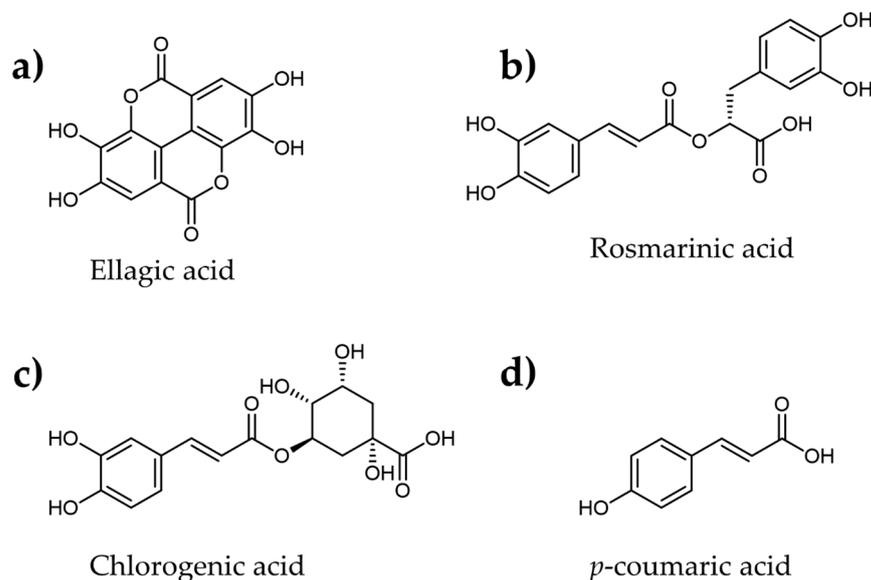

Figure 7. Molecular structures of various plant-derived phenolic acids identified as α-amylase inhibitors.

4.5. Tannins

Tannins are polyphenolic biomolecules that have the tendency to precipitate proteins in water. They are widely available in many plant species and act as growth regulators and protectors against plant predators [186]. In traditional folk medicine, a variety of tannin-rich plants are frequently used by diabetic patients to treat diabetes mellitus and its associated issues [187].

Wang et al. [153] studied the in vitro α-amylase inhibition of Chinese bayberry leaf-derived proanthocyanidins (BLPs) and found that BLPs could retard the activity of an α-amylase enzyme using a mixed-type inhibition mode with an IC_{50} of 3.07 µg/mL. Chen et al. [151] identified twenty-five major ellagitannins from the unripe fruit of *Rubus chingii* Hu. Among them, chingiitannin A (Figure 8a) demonstrated around seven times higher inhibition with an IC_{50} of 4.52 µM compared to acarbose (IC_{50} = 35.71 µM). Moreover, molecular docking studies revealed that chingiitannin A binds at the allosteric site and primarily bonds with the enzymes through hydrogen bonds. Furthermore, chingiitannin A was non-toxic and improved glucose absorption. Similarly, 1,2,3,4,6-penta-*O*-galloyl-β-D-glucopyranose (Figure 8b), from the leaves of *Rhus coriaria*, was reported to exhibit higher inhibitory effects on an α-amylase enzyme with an IC_{50} of 6.32 µM than acarbose (IC_{50} = 10.69 µM) [70]. However, more scientific analysis is necessary to determine the in vivo anti-diabetic effect of these tannins, and an assessment of toxicity should be performed in order to design therapeutic biomolecules with no or very few side effects.
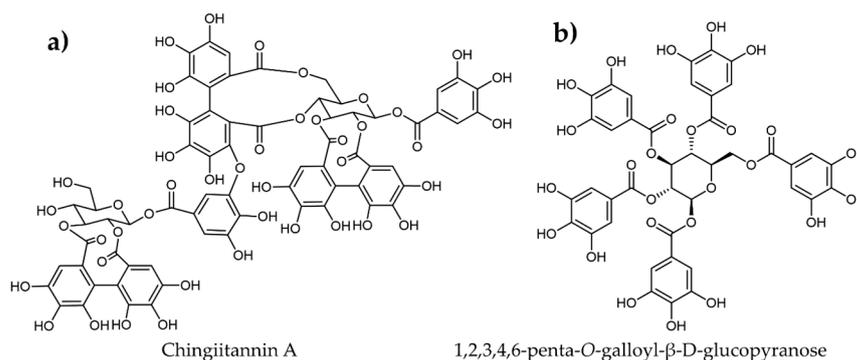
Figure 8. Molecular structures of various plant-derived tannins identified as α-amylase inhibitors.

4.6. Miscellaneous Secondary Metabolites as α-Amylase Inhibitors

Plants possess various bioactive compounds with different structural moieties, which demonstrated efficient α-amylase inhibition. For example, Thuy and his co-workers isolated three new pregnane glycosides from *Dregea volubilis* leaves, among which Drevoluoside Q exhibited significant inhibitory effects against α-amylase (IC_{50} = 51.3 µM), which is comparable to acarbose (IC_{50} = 36.3 µM) [157]. Likewise, phytochemical studies of another plant species, *Gymnema sylvestre*, resulted in the separation of five new pregnane glycosides, known as gymsylodide A, gymsylodide B, gymsylodide C, gymsylodide D, and gymsylodide E. Among them, gymsylodides B-E were found to have considerable α-amylase inhibitory action, with half-maximal inhibitory concentrations ranging from 113.0 to 176.2 µM [158].

An alkaloid, 3,3′,5,5′,8-pentamethyl-3,3′-bis(4-methylpent-3-en-1-yl)-3,3′,11,11′-tetrahydro-10,10′-bipyrano[3,2-*a*]carbazole (Figure 9a), was identified from *Murraya koenigii* leaves, which displayed significant in vitro α-amylase inhibition with an IC_{50} of 30.32 ppm [155]. Similarly, another known alkaloid, berberine (Figure 9b), was isolated from the *Cardiospermum halicacabum* plant and found to retard the activity of α-amylase by 72% at 10 µg/mL. In addition, in silico investigations indicated that berberine adheres to the enzyme's active site [156].

Another class of bioactive molecules, xanthones named garcixanthone D and garcinone E (Figure 9c), were purified from the pericarp of *Garcinia mangostana* and showed 93.8 and 85.6% inhibition against α-amylase, respectively. The molecular docking studies revealed that these two compounds interact with α-amylase differently than the standard acarbose [160]. Similarly, a new prenylated xanthone, mangoxanthone A, with a moderate α-amylase inhibitory effect (IC_{50} = 22.74 µM), was reported from *Garcinia mangostana* pericarp [159].

Makinde et al. [162] discovered a fatty acid derivative, 5,7-dihydroxy-6-oxoheptadecanoic acid (Figure 9d), from the *Tiliacora triandra* plant that inhibited α-amylase enzymes (IC_{50} = 26.27 µM) more effectively than acarbose (IC_{50} = 177.65 µM). Halfordin (Figure 9e), a coumarin molecule purified from the bark extract of *Melicope latifolia*, was investigated for its potential to inhibit α-amylase enzymes [71] and was shown to be effective (IC50 = 197.53 µM). In addition, in silico investigations revealed a large number of molecular interactions with key α-amylase amino acid residues. Moreover, β-Sitosterol (Figure 9f) was identified as an effective α-amylase inhibitor from *Parthenium hysterophorus* leaf extract [163]. According to the molecular dynamics analyses, β-sitosterol has a larger binding energy than acarbose and the highest stability with α-amylase enzymes.
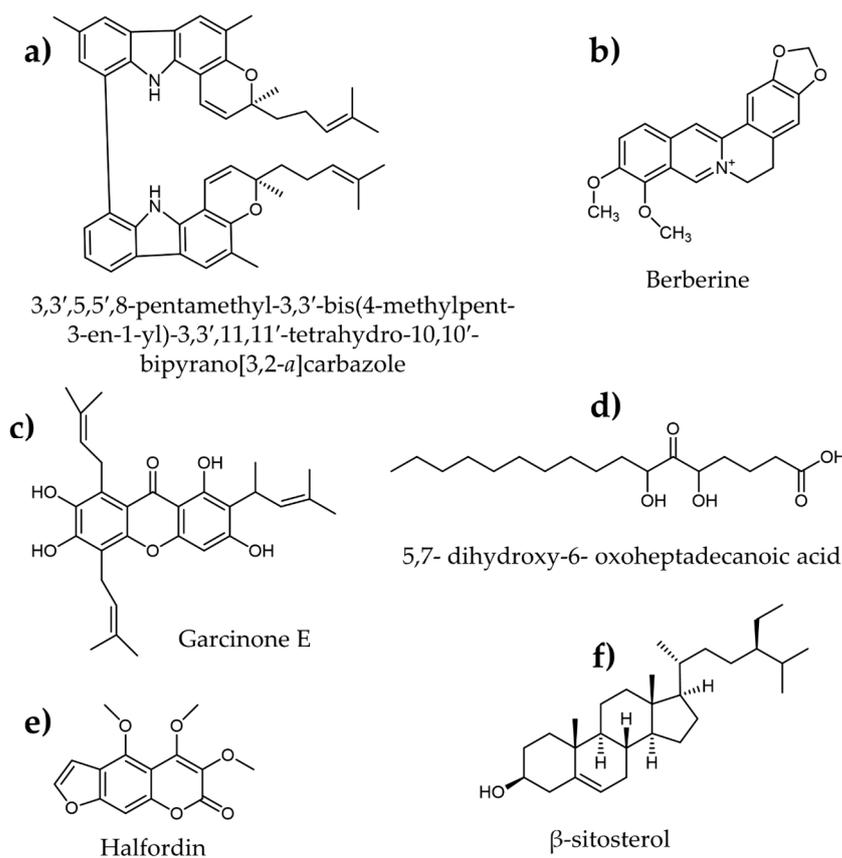
a) 3,3′,5,5′,8-pentamethyl-3,3′-bis(4-methylpent-3-en-1-yl)-3,3′,11,11′-tetrahydro-10,10′-bipyrano[3,2-*a*]carbazole

b) Berberine

c) Garcinone E

d) 5,7- dihydroxy-6- oxoheptadecanoic acid

e) Halfordin

f) β-sitosterol

Figure 9. Molecular structures of various plant-derived secondary metabolites identified as α-amylase inhibitors.

Investigations into natural compounds with significant α-amylase inhibitory effects are critical since many phytocompounds are consumed in the form of food in our daily lives. Based on findings on their potential effectiveness in inhibiting α-amylase enzymes, bioactive natural compounds are thought to play a very critical role in diabetes treatment. As a result, more research and analyses are needed to assess the toxic effect as well as other drug interactions or unfavorable effects that they might create in in vivo studies. Furthermore, additional human clinical trials are required to validate the safety and anti-diabetic benefits of α-amylase inhibitors derived from various plant species.

5. Conclusions

Diabetes is a chronic metabolic illness recognized by persistently elevated blood sugar levels resulting from a decrease in insulin synthesis or a rise in insulin resistance. One preliminary-stage diabetes therapy technique is to lessen post-meal hyperglycemia. This can be accomplished by moderating the bioactivity of α-amylases, carbohydrate-digestive enzymes that hinder glucose absorption in the gut. Consequently, inhibitors of these enzymes limit the rate of glucose absorption, lowering postprandial plasma glucose levels. Growing evidence from traditional and herbal approaches to diabetes management indicates that plant extracts and their chemical components may play a substantial role in the therapeutic management of T2D and its implications. Hence, this review study aimed to summarize the latest and most advanced findings in natural product research that operate as α-amylase enzyme inhibitors. Despite the fact that scientists have put in a lot of effort to identify the inhibitory effects of various plant extracts and natural compounds against the α-amylase enzyme, there are still some gaps. The majority of research focuses on in vitro investigations of the inhibitory effect of plant extracts and the identification of bioactive molecules. However, only a very limited amount of additional study was conducted for in vivo tests in animals, and human trials were extremely rare. Therefore,

more research and scientific analyses are needed to assimilate the pharmacological activity of natural extracts and compounds, the synergistic effects of active compounds with other molecules, and their safer use. Moreover, clinical trials are crucial for reaching precise conclusions on both the safety and effectiveness of administering plant extracts or active compounds for the management of type 2 diabetes. Prospective studies will offer important information for determining the doses of natural extracts and active compounds that will deliver the desired therapeutic advantages while exhibiting little to no adverse side effects. This study explored over fifty extracts obtained with various solvents and over sixty natural ingredients. The insights gained from this review's findings should help to achieve the ultimate goal of developing new therapeutic drugs with improved effectiveness and safety for the management of T2D or to avoid PPHG.

Author Contributions: Conceptualization, H.K.; Writing—original draft preparation, H.K.; Writing—review and editing, K.-H.B.; Funding acquisition, K.-H.B. All authors have read and agreed to the published version of the manuscript.

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

References

1. Kahn, S.E.; Cooper, M.E.; Del Prato, S. Pathophysiology and Treatment of Type 2 Diabetes: Perspectives on the Past, Present, and Future. *Lancet* **2014**, *383*, 1068–1083. [CrossRef] [PubMed]
2. Kharroubi, A.T. Diabetes Mellitus: The Epidemic of the Century. *World J. Diabetes* **2015**, *6*, 850. [CrossRef] [PubMed]
3. Eizirik, D.L.; Pasquali, L.; Cnop, M. Pancreatic β-Cells in Type 1 and Type 2 Diabetes Mellitus: Different Pathways to Failure. *Nat. Rev. Endocrinol.* **2020**, *16*, 349–362. [CrossRef]
4. Pinhas-Hamiel, O.; Zeitler, P. Acute and Chronic Complications of Type 2 Diabetes Mellitus in Children and Adolescents. *Lancet* **2007**, *369*, 1823–1831. [CrossRef] [PubMed]
5. Forbes, J.M.; Cooper, M.E. Mechanisms of Diabetic Complications. *Physiol. Rev.* **2013**, *93*, 137–188. [CrossRef]
6. Association, A.D. Standards of Medical Care in Diabetes—2014. *Diabetes Care* **2014**, *37*, S14–S80. [CrossRef]
7. American Diabetes Association Professional Practice Committee. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2022. *Diabetes Care* **2022**, *45*, S17–S38. [CrossRef]
8. Danaei, G.; Finucane, M.M.; Lu, Y.; Singh, G.M.; Cowan, M.J.; Paciorek, C.J.; Lin, J.K.; Farzadfar, F.; Khang, Y.-H.; Stevens, G.A.; et al. National, Regional, and Global Trends in Fasting Plasma Glucose and Diabetes Prevalence since 1980: Systematic Analysis of Health Examination Surveys and Epidemiological Studies with 370 Country-Years and 2·7 Million Participants. *Lancet* **2011**, *378*, 31–40. [CrossRef]
9. International Diabetes Federation. *IDF Diabetes Atlas*, 10th ed.; IDF: Brussels, Belgium, 2021; Available online: https://diabetesatlas.org/idfawp/resource-files/2021/07/idf_atlas_10th_edition_2021.pdf (accessed on 1 May 2023).
10. Alberti, K.G.M.M.; Zimmet, P.Z. Definition, Diagnosis and Classification of Diabetes Mellitus and Its Complications. Part 1: Diagnosis and Classification of Diabetes Mellitus. Provisional Report of a WHO Consultation. *Diabet. Med.* **1998**, *15*, 539–553. [CrossRef]
11. Holman, R.R.; Paul, S.K.; Bethel, M.A.; Matthews, D.R.; Neil, H.A.W. 10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes. *N. Engl. J. Med.* **2008**, *359*, 1577–1589. [CrossRef]
12. Papoutsis, K.; Zhang, J.; Bowyer, M.C.; Brunton, N.; Gibney, E.R.; Lyng, J. Fruit, Vegetables, and Mushrooms for the Preparation of Extracts with α-Amylase and α-Glucosidase Inhibition Properties: A Review. *Food Chem.* **2021**, *338*, 128119. [CrossRef]
13. Tundis, R.; Loizzo, M.R.M.R.; Menichini, F. Natural Products as α-Amylase and & α-Glucosidase Inhibitors and Their Hypoglycaemic Potential in the Treatment of Diabetes: An Update. *Mini-Rev. Med. Chem.* **2010**, *10*, 315–331. [CrossRef] [PubMed]
14. Watanabe, J.; Kawabata, J.; Kurihara, H.; Niki, R. Isolation and Identification of α-Glucosidase Inhibitors from Tochu-Cha (Eucommia Ulmoides). *Biosci. Biotechnol. Biochem.* **1997**, *61*, 177–178. [CrossRef] [PubMed]
15. Horii, S.; Fukase, H.; Matsuo, T.; Kameda, Y.; Asano, N.; Matsui, K. Synthesis and. Alpha.-D-Glucosidase Inhibitory Activity of N-Substituted Valiolamine Derivatives as Potential Oral Antidiabetic Agents. *J. Med. Chem.* **1986**, *29*, 1038–1046. [CrossRef] [PubMed]
16. Laar, F. Alpha-Glucosidase Inhibitors in the Early Treatment of Type 2 Diabetes. *Vasc. Health Risk Manag.* **2008**, *4*, 1189–1195. [CrossRef]
17. Van de Laar, F.A.; Lucassen, P.L.; Akkermans, R.P.; Van de Lisdonk, E.H.; Rutten, G.E.; Van Weel, C. Alpha-Glucosidase Inhibitors for Type 2 Diabetes Mellitus. *Cochrane Database Syst. Rev.* **2005**, *2009*. [CrossRef]

18. Ho, P.M.; Rumsfeld, J.S.; Masoudi, F.A.; McClure, D.L.; Plomondon, M.E.; Steiner, J.F.; Magid, D.J. Effect of Medication Nonadherence on Hospitalization and Mortality among Patients with Diabetes Mellitus. *Arch. Intern. Med.* **2006**, *166*, 1836. [CrossRef]

19. Kashtoh, H.; Hussain, S.; Khan, A.; Saad, S.M.; Khan, J.A.J.; Khan, K.M.; Perveen, S.; Choudhary, M.I. Oxadiazoles and Thiadiazoles: Novel α-Glucosidase Inhibitors. *Bioorganic Med. Chem.* **2014**, *22*, 5454–5465. [CrossRef]

20. Niaz, H.; Kashtoh, H.; Khan, J.A.J.; Khan, A.; Wahab, A.T.; Alam, M.T.; Khan, K.M.; Perveen, S.; Choudhary, M.I. Synthesis of Diethyl 4-Substituted-2,6-Dimethyl-1,4-Dihydropyridine-3,5-Dicarboxylates as a New Series of Inhibitors against Yeast α-Glucosidase. *Eur. J. Med. Chem.* **2015**, *95*, 199–209. [CrossRef]

21. Kashtoh, H.; Muhammad, M.T.; Khan, J.J.A.; Rasheed, S.; Khan, A.; Perveen, S.; Javaid, K.; Atia-Tul-Wahab; Khan, K.M.; Choudhary, M.I. Dihydropyrano [2,3-c] Pyrazole: Novel in Vitro Inhibitors of Yeast α-Glucosidase. *Bioorg. Chem.* **2016**, *65*, 61–72. [CrossRef]

22. Zhang, X.; World Health Organization. *Traditional Medicine Strategy 2002–2005*; World Health Organization: Geneva, Switzerland, 2002.

23. Al-Aboudi, A.; Afifi, F.U. Plants Used for the Treatment of Diabetes in Jordan: A Review of Scientific Evidence. *Pharm. Biol.* **2011**, *49*, 221–239. [CrossRef]

24. World Health Organization. *WHO Expert Committee on Diabetes Mellitus [Meeting Held in Geneva from 25 September to 1 October 1979]: Second Report*; World Health Organization: Geneva, Switzerland, 1980; ISBN 9241206462.

25. Butterworth, P.J.; Warren, F.J.; Ellis, P.R. Human α-Amylase and Starch Digestion: An Interesting Marriage. *Starch—Stärke* **2011**, *63*, 395–405. [CrossRef]

26. Patel, H.; Royall, P.G.; Gaisford, S.; Williams, G.R.; Edwards, C.H.; Warren, F.J.; Flanagan, B.M.; Ellis, P.R.; Butterworth, P.J. Structural and Enzyme Kinetic Studies of Retrograded Starch: Inhibition of α-Amylase and Consequences for Intestinal Digestion of Starch. *Carbohydr. Polym.* **2017**, *164*, 154–161. [CrossRef] [PubMed]

27. Svensson, B. Regional Distant Sequence Homology between Amylases, α-Glucosidases and Transglucanosylases. *FEBS Lett.* **1988**, *230*, 72–76. [CrossRef]

28. Henrissat, B. A Classification of Glycosyl Hydrolases Based on Amino Acid Sequence Similarities. *Biochem. J.* **1991**, *280*, 309–316. [CrossRef] [PubMed]

29. Plaunt, A.J.; de Lourdes Betancourt-Mendiola, M.; Smith, B.D. Biomolecule Recognition Using Transition Metal Ions and Hydrogen Bonding. In *Comprehensive Supramolecular Chemistry II*; Elsevier: Amsterdam, The Netherlands, 2017; pp. 575–591. [CrossRef]

30. Steer, M.L.; Levitzki, A. The Metal Specificity of Mammalian α-Amylase as Revealed by Enzyme Activity and Structural Probes. *FEBS Lett.* **1973**, *31*, 89–92. [CrossRef]

31. Vallee, B.L.; Stein, E.A.; Sumerwell, W.N.; Fischer, E.H. Metal Content of α-Amylases of Various Origins. *J. Biol. Chem.* **1959**, *234*, 2901–2905. [CrossRef]

32. Levitzki, A.; Steer, M.L. The Allosteric Activation of Mammalian Alpha-Amylase by Chloride. *Eur. J. Biochem.* **1974**, *41*, 171–180. [CrossRef]

33. Brayer, G.D.; Luo, Y.; Withers, S.G. The Structure of Human Pancreatic α-Amylase at 1.8 Å Resolution and Comparisons with Related Enzymes. *Protein Sci.* **1995**, *4*, 1730–1742. [CrossRef]

34. Gumucio, D.L.; Wiebauer, K.; Caldwell, R.M.; Samuelson, L.C.; Meisler, M.H. Concerted Evolution of Human Amylase Genes. *Mol. Cell. Biol.* **1988**, *8*, 1197–1205. [CrossRef] [PubMed]

35. Sales, P.M.; Souza, P.M.; Simeoni, L.A.; Magalhães, P.O.; Silveira, D. α-Amylase Inhibitors: A Review of Raw Material and Isolated Compounds from Plant Source. *J. Pharm. Pharm. Sci.* **2012**, *15*, 141. [CrossRef] [PubMed]

36. Liu, D.; Gao, H.; Tang, W.; Nie, S. Plant Non-Starch Polysaccharides That Inhibit Key Enzymes Linked to Type 2 Diabetes Mellitus. *Ann. N. Y. Acad. Sci.* **2017**, *1401*, 28–36. [CrossRef] [PubMed]

37. Martinez-Gonzalez, A.I.; Díaz-Sánchez, Á.G.; de la Rosa, L.A.; Vargas-Requena, C.L.; Bustos-Jaimes, I.; Alvarez-Parrilla, E. Polyphenolic Compounds and Digestive Enzymes: In Vitro Non-Covalent Interactions. *Molecules* **2017**, *22*, 669. [CrossRef]

38. Brayer, G.D.; Sidhu, G.; Maurus, R.; Rydberg, E.H.; Braun, C.; Wang, Y.; Nguyen, N.T.; Overall, C.M.; Withers, S.G. Subsite Mapping of the Human Pancreatic α-Amylase Active Site through Structural, Kinetic, and Mutagenesis Techniques. *Biochemistry* **2000**, *39*, 4778–4791. [CrossRef]

39. Dhital, S.; Warren, F.J.; Butterworth, P.J.; Ellis, P.R.; Gidley, M.J. Mechanisms of Starch Digestion by α-Amylase—Structural Basis for Kinetic Properties. *Crit. Rev. Food Sci. Nutr.* **2017**, *57*, 875–892. [CrossRef]

40. Truscheit, E.; Frommer, W.; Junge, B.; Müller, L.; Schmidt, D.D.; Wingender, W. Chemistry and Biochemistry of Microbial α-Glucosidase Inhibitors. *Angew. Chemie Int. Ed. Engl.* **1981**, *20*, 744–761. [CrossRef]

41. Nichols, B.L.; Avery, S.; Sen, P.; Swallow, D.M.; Hahn, D.; Sterchi, E. The Maltase-Glucoamylase Gene: Common Ancestry to Sucrase-Isomaltase with Complementary Starch Digestion Activities. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 1432–1437. [CrossRef]

42. Williamson, G. Possible Effects of Dietary Polyphenols on Sugar Absorption and Digestion. *Mol. Nutr. Food Res.* **2013**, *57*, 48–57. [CrossRef]

43. Ramasubbu, N.; Paloth, V.; Luo, Y.; Brayer, G.D.; Levine, M.J. Structure of Human Salivary α-Amylase at 1.6 Å Resolution: Implications for Its Role in the Oral Cavity. *Acta Crystallogr. Sect. D Biol. Crystallogr.* **1996**, *52*, 435–446. [CrossRef]

44. Gilles, C.; Astier, J.; Marchis-Mouren, G.; Cambillau, C.; Payan, F. Crystal Structure of Pig Pancreatic Alpha-Amylase Isoenzyme II, in Complex with the Carbohydrate Inhibitor Acarbose. *Eur. J. Biochem.* **1996**, *238*, 561–569. [CrossRef] [PubMed]

45. Lifshitz, R.; Levitzki, A. Identity and Properties of the Chloride Effector Binding Site in Hog Pancreatic α-Amylase. *Biochemistry* **1976**, *15*, 1987–1993. [CrossRef]

46. MacGregor, E.A.; Janeček, Š.; Svensson, B. Relationship of Sequence and Structure to Specificity in the α-Amylase Family of Enzymes. *Biochim. Biophys. Acta—Protein Struct. Mol. Enzymol.* **2001**, *1546*, 1–20. [CrossRef]

47. Schrödinger, L.L.C.; DeLano, W. Pymol. *PyMOL Mol. Graph. Syst. Version* **2020**, *2*. Available online: https://pymol.org/2/support.html? (accessed on 1 April 2022).

48. Nahoum, V.; Roux, G.; Anton, V.; Rougé, P.; Puigserver, A.; Bischoff, H.; Henrissat, B.; Payan, F. Crystal Structures of Human Pancreatic α-Amylase in Complex with Carbohydrate and Proteinaceous Inhibitors. *Biochem. J.* **2000**, *346*, 201–208. [CrossRef]

49. Aghajari, N.; Feller, G.; Gerday, C.; Haser, R. Structural Basis of α-Amylase Activation by Chloride. *Protein Sci.* **2002**, *11*, 1435–1441. [CrossRef]

50. Qian, M.; Haser, R.; Buisson, G.; Duee, E.; Payan, F. The Active Center of a Mammalian .Alpha.-Amylase. Structure of the Complex of a Pancreatic. Alpha.-Amylase with a Carbohydrate Inhibitor Refined to 2.2-.ANG. Resolution. *Biochemistry* **1994**, *33*, 6284–6294. [CrossRef] [PubMed]

51. Feller, G.; le Bussy, O.; Houssier, C.; Gerday, C. Structural and Functional Aspects of Chloride Binding to Alteromonas Haloplanctis α-Amylase. *J. Biol. Chem.* **1996**, *271*, 23836–23841. [CrossRef]

52. Robyt, J.F. Starch: Structure, Properties, Chemistry, and Enzymology. In *Glycoscience*; Springer: Berlin/Heidelberg, Germany, 2008; pp. 1437–1472. [CrossRef]

53. Robyt, J.F.; French, D. Multiple Attack Hypothesis of α-Amylase Action: Action of Porcine Pancreatic, Human Salivary, and Aspergillus Oryzae α-Amylases. *Arch. Biochem. Biophys.* **1967**, *122*, 8–16. [CrossRef] [PubMed]

54. Seigner, C.; Prodanov, E.; Marchis-Mouren, G. The Determination of Subsite Binding Energies of Porcine Pancreatic α-Amylase by Comparing Hydrolytic Activity towards Substrates. *Biochim. Biophys. Acta—Protein Struct. Mol. Enzymol.* **1987**, *913*, 200–209. [CrossRef]

55. Jarald, E.; Joshi, S.B.; Jain, D. Diabetes and Herbal Medicines. *Pharmacol. Ther.* **2008**, *7*, 97–106.

56. Hamdan, I.; Afifi, F. Studies on the in Vitro and in Vivo Hypoglycemic Activities of Some Medicinal Plants Used in Treatment of Diabetes in Jordanian Traditional Medicine. *J. Ethnopharmacol.* **2004**, *93*, 117–121. [CrossRef] [PubMed]

57. Tag, H.; Kalita, P.; Dwivedi, P.; Das, A.K.; Namsa, N.D. Herbal Medicines Used in the Treatment of Diabetes Mellitus in Arunachal Himalaya, Northeast, India. *J. Ethnopharmacol.* **2012**, *141*, 786–795. [CrossRef] [PubMed]

58. Bailey, C.J.; Day, C. Traditional Plant Medicines as Treatments for Diabetes. *Diabetes Care* **1989**, *12*, 553–564. [CrossRef] [PubMed]

59. Baharvand-Ahmadi, B.; Bahmani, M.; Tajeddini, P.; Naghdi, N.; Rafieian-Kopaei, M. An Ethno-Medicinal Study of Medicinal Plants Used for the Treatment of Diabetes. *J. Nephropathol.* **2015**, *5*, 44–50. [CrossRef]

60. Giovannini, P.; Howes, M.-J.R.; Edwards, S.E. Medicinal Plants Used in the Traditional Management of Diabetes and Its Sequelae in Central America: A Review. *J. Ethnopharmacol.* **2016**, *184*, 58–71. [CrossRef]

61. Moreira, D.D.L.; Teixeira, S.S.; Monteiro, M.H.D.; De-Oliveira, A.C.A.X.; Paumgartten, F.J.R. Traditional Use and Safety of Herbal Medicines. *Rev. Bras. Farmacogn.* **2014**, *24*, 248–257. [CrossRef]

62. Ekor, M. The Growing Use of Herbal Medicines: Issues Relating to Adverse Reactions and Challenges in Monitoring Safety. *Front. Pharmacol.* **2014**, *4*, 177. [CrossRef]

63. Daoudi, N.E.; Bouhrim, M.; Ouassou, H.; Legssyer, A.; Mekhfi, H.; Ziyyat, A.; Aziz, M.; Bnouham, M. Inhibitory Effect of Roasted/Unroasted *Argania spinosa* Seeds Oil on α- Glucosidase, α-Amylase and Intestinal Glucose Absorption Activities. *S. Afr. J. Bot.* **2020**, *135*, 413–420. [CrossRef]

64. Quek, A.; Kassim, N.K.; Ismail, A.; Latif, M.A.M.; Shaari, K.; Tan, D.C.; Lim, P.C. Identification of Dipeptidyl Peptidase-4 and α-Amylase Inhibitors from *Melicope glabra* (Blume) TG Hartley (Rutaceae) Using Liquid Chromatography Tandem Mass Spectrometry, In Vitro and In Silico Methods. *Molecules* **2020**, *26*, 1. [CrossRef]

65. Tekulu, G.H.; Araya, E.M.; Mengesha, H.G. In Vitro α-Amylase Inhibitory Effect of TLC Isolates of *Aloe megalacantha* Baker and *Aloe monticola* Reynolds. *BMC Complement. Altern. Med.* **2019**, *19*, 206. [CrossRef] [PubMed]

66. Panigrahy, S.K.; Kumar, A.; Bhatt, R. *Hedychium coronarium* Rhizomes: Promising Antidiabetic and Natural Inhibitor of α-Amylase and α-Glucosidase. *J. Diet. Suppl.* **2020**, *17*, 81–87. [CrossRef] [PubMed]

67. Hawash, M.; Jaradat, N.; Elaraj, J.; Hamdan, A.; Lebdeh, S.A.; Halawa, T. Evaluation of the Hypoglycemic Effect of Seven Wild Folkloric Edible Plants from Palestine (Antidiabetic Effect of Seven Plants from Palestine). *J. Complement. Integr. Med.* **2020**, *17*, 1–10. [CrossRef]

68. Sansenya, S.; Payaka, A.; Wannasut, W.; Hua, Y.; Chumanee, S. Biological Activity of Rice Extract and the Inhibition Potential of Rice Extract, Rice Volatile Compounds and Their Combination against α-Glucosidase, α-Amylase and Tyrosinase. *Int. J. Food Sci. Technol.* **2021**, *56*, 1865–1876. [CrossRef]

69. Xu, S.; Qin, L.; Mazhar, M.; Zhu, Y. Functional Components Profile and Glycemic Index of Kidney Beans. *Front. Nutr.* **2022**, *9*, 1044427. [CrossRef] [PubMed]

70. Gök, H.N.; Deliorman Orhan, D.; Gürbüz, İ.; Aslan, M. Activity-Guided Isolation of α-Amylase, α-Glucosidase, and Pancreatic Lipase Inhibitory Compounds from *Rhus coriaria* L. *J. Food Sci.* **2020**, *85*, 3220–3228. [CrossRef] [PubMed]

71. Quek, A.; Kassim, N.K.; Lim, P.C.; Tan, D.C.; Mohammad Latif, M.A.; Ismail, A.; Shaari, K.; Awang, K. α-Amylase and Dipeptidyl Peptidase-4 (DPP-4) Inhibitory Effects of *Melicope latifolia* Bark Extracts and Identification of Bioactive Constituents Using in Vitro and in Silico Approaches. *Pharm. Biol.* **2021**, *59*, 964–973. [CrossRef]

72. Sani, D.H.; Munna, A.N.; Alam, M.J.; Salim, M.; Alam, M.J. Evaluation of α-Amylase Inhibition and Cytotoxic Activities of the *Arachis hypogaea* and *Cinnamomum tamala*. *Curr. Nutr. Food Sci.* **2020**, *17*, 328–336. [CrossRef]

73. Romero Rocamora, C.; Ramasamy, K.; Meng Lim, S.; Majeed, A.B.A.; Agatonovic-Kustrin, S. HPTLC Based Approach for Bioassay-Guided Evaluation of Antidiabetic and Neuroprotective Effects of Eight Essential Oils of the Lamiaceae Family Plants. *J. Pharm. Biomed. Anal.* **2020**, *178*, 112909. [CrossRef]

74. Wu, M.; Yang, Q.; Wu, Y.; Ouyang, J. Inhibitory Effects of Acorn (*Quercus variabilis* Blume) Kernel-Derived Polyphenols on the Activities of α-Amylase, α-Glucosidase, and Dipeptidyl Peptidase IV. *Food Biosci.* **2021**, *43*, 101224. [CrossRef]

75. Sen, A.; Kurkcuoglu, M.; Yildirim, A.; Senkardes, I.; Bitis, L.; Baser, K.H.C. Chemical Composition, Antiradical, and Enzyme Inhibitory Potential of Essential Oil Obtained from Aerial Part of *Centaurea pterocaula* Trautv. *J. Essent. Oil Res.* **2021**, *33*, 44–52. [CrossRef]

76. Paun, G.; Neagu, E.; Albu, C.; Savin, S.; Radu, G.L. In Vitro Evaluation of Antidiabetic and Anti-Inflammatory Activities of Polyphenolic-Rich Extracts from *Anchusa officinalis* and *Melilotus officinalis*. *ACS Omega* **2020**, *5*, 13014–13022. [CrossRef] [PubMed]

77. Hoang Anh, L.; Xuan, T.D.; Dieu Thuy, N.T.; Van Quan, N.; Trang, L.T. Antioxidant and α-Amylase Inhibitory Activities and Phytocompounds of *Clausena indica* Fruits. *Medicines* **2020**, *7*, 10. [CrossRef]

78. Kumar, M.; Govindasamy, J.; Nyola, N.K. In-Vitro and in-Vivo Anti-Hyperglycemic Potential of *Prosopis cineraria* Pods Extract and Fractions. *J. Biol. Act. Prod. Nat.* **2019**, *9*, 135–140. [CrossRef]

79. Prasathkumar, M.; Raja, K.; Vasanth, K.; Khusro, A.; Sadhasivam, S.; Sahibzada, M.U.K.; Gawwad, M.R.A.; Al Farraj, D.A.; Elshikh, M.S. Phytochemical Screening and in Vitro Antibacterial, Antioxidant, Anti-Inflammatory, Anti-Diabetic, and Wound Healing Attributes of *Senna auriculata* (L.) Roxb. Leaves. *Arab. J. Chem.* **2021**, *14*, 103345. [CrossRef]

80. Al-Ahmed, A.; Khalil, H.E. Antidiabetic Activity of Terfeziaclaveryi; An in Vitro and in Vivo Study. *Biomed. Pharmacol. J.* **2019**, *12*, 603–608. [CrossRef]

81. Prakash, V. Determination of α-Amylase Inhibitory Potential of Leaf Extracts of *Rhododendron arboreum* Sm. and *Rhododendron campanulatum* D. Don. *J. Drug Deliv. Ther.* **2022**, *12*, 20–22. [CrossRef]

82. Mazumder, K.; Sumi, T.S.; Golder, M.; Biswas, B.; Maknoon; Kerr, P.G. Antidiabetic Profiling, Cytotoxicity and Acute Toxicity Evaluation of Aerial Parts of *Phragmites karka* (Retz.). *J. Ethnopharmacol.* **2021**, *270*, 113781. [CrossRef]

83. da Silva, D.H.A.; Barbosa, H.d.M.; Beltrão, R.L.d.A.; Silva, C.d.F.O.; Moura, C.A.; Castro, R.N.; Almeida, J.R.G.d.S.; Gomes, D.A.; Lira, E.C. Hexane Fraction from Brazilian *Morus nigra* Leaves Improved Oral Carbohydrate Tolerance and Inhibits α-Amylase and α-Glucosidase Activities in Diabetic Mice. *Nat. Prod. Res.* **2021**, *35*, 4785–4788. [CrossRef]

84. Ktari, N.; Ben Slama-Ben Salem, R.; Bkhairia, I.; Ben Slima, S.; Nasri, R.; Ben Salah, R.; Nasri, M. Functional Properties and Biological Activities of Peptides from Zebra Blenny Protein Hydrolysates Fractionated Using Ultrafiltration. *Food Biosci.* **2020**, *34*, 100539. [CrossRef]

85. Renganathan, S.; Manokaran, S.; Vasanthakumar, P.; Singaravelu, U.; Kim, P.S.; Kutzner, A.; Heese, K. Phytochemical Profiling in Conjunction with in Vitro and in Silico Studies to Identify Human α-Amylase Inhibitors in *Leucaena leucocephala* (Lam.) de Wit for the Treatment of Diabetes Mellitus. *ACS Omega* **2021**, *6*, 19045–19057. [CrossRef] [PubMed]

86. Pandey, B.P.; Pradhan, S.P.; Adhikari, K.; Nepal, S. *Bergenia pacumbis* from Nepal, an Astonishing Enzymes Inhibitor. *BMC Complement. Med. Ther.* **2020**, *20*, 198. [CrossRef]

87. Jaradat, N.; Abualhasan, M.N.; Qadi, M.; Issa, L.; Mousa, A.; Allan, F.; Hindi, M.; Alhrezat, Z. Antiamylase, Antilipase, Antimicrobial, and Cytotoxic Activity of *Nonea obtusifolia* (Willd.) Dc. From Palestine. *Biomed Res. Int.* **2020**, *2020*, 8821319. [CrossRef] [PubMed]

88. Jan, B.; Zahiruddin, S.; Basist, P.; Irfan, M.; Abass, S.; Ahmad, S. Metabolomic Profiling and Identification of Antioxidant and Antidiabetic Compounds from Leaves of Different Varieties of *Morus alba Linn* Grown in Kashmir. *ACS Omega* **2022**, *7*, 24317–24328. [CrossRef]

89. Omar, R.M.; Badria, F.A.; Galala, A.A. An Emerging Flavone Glycoside from *Phyllanthus emblica* L.: As Promiscuous Enzyme Inhibitor and Potential Therapeutic in Chronic Diseases. *S. Afr. J. Bot.* **2023**, *153*, 290–296. [CrossRef]

90. Timalsina, D.; Bhusal, D.; Devkota, H.P.; Pokhrel, K.P.; Sharma, K.R. α-Amylase Inhibitory Activity of *Catunaregam spinosa* (Thunb.) Tirveng.: In Vitro and in Silico Studies. *Biomed Res. Int.* **2021**, *2021*, 4133876. [CrossRef]

91. Choudhary, N.; Prabhakar, P.K.; Khatik, G.L.; Chamakuri, S.R.; Tewari, D.; Suttee, A. Evaluation of Acute Toxicity, in-Vitro, in-Vivo Antidiabetic Potential of the Flavonoid Fraction of the Plant *Chenopodium album* L. *Pharmacogn. J.* **2021**, *13*, 765–779. [CrossRef]

92. Saraswathi, K.; Bharkavi, R.; Khusro, A.; Sivaraj, C.; Arumugam, P.; Alghamdi, S.; Dablool, A.S.; Almehmadi, M.; Bannunah, A.M.; Umar Khayam Sahibzada, M. Assessment on in Vitro Medicinal Properties and Chemical Composition Analysis of *Solanum virginianum* Dried Fruits. *Arab. J. Chem.* **2021**, *14*, 103442. [CrossRef]

93. Bello, M.; Jiddah-kazeem, B.; Fatoki, T.H.; Ibukun, E.O.; Akinmoladun, A.C. Antioxidant Property of *Eucalyptus globulus* Labill. Extracts and Inhibitory Activities on Carbohydrate Metabolizing Enzymes Related to Type-2 Diabetes. *Biocatal. Agric. Biotechnol.* **2021**, *36*, 102111. [CrossRef]

94. Mikailu, S.; Okorafor, M.C.; Abo, K.A. Alpha-Amylase Inhibition and Membrane Stabilizing Effect of the Stem Bark of *Maesobotrya dusenii* Hutchinson. *Int. J. Pharm. Sci. Res.* **2019**, *10*, 5154–5159. [CrossRef]

95. Hassan, A.; Khan Mohmand, N.Z.; Ullah, H.; Hussain, A. Antioxidant, Antidiabetic, and Antihypertension Inhibitory Potentials of Phenolic Rich Medicinal Plants. *J. Chem.* **2022**, *2022*, 9046780. [CrossRef]

96. Remok, F.; Saidi, S.; Gourich, A.A.; Zibouh, K.; Maouloua, M.; El Makhoukhi, F.; El Menyiy, N.; Touijer, H.; Bouhrim, M.; Sahpaz, S.; et al. Phenolic Content, Antioxidant, Antibacterial, Antihyperglycemic, and α-Amylase Inhibitory Activities of Aqueous Extract of *Salvia lavandulifolia* Vahl. *Pharmaceuticals* **2023**, *16*, 395. [CrossRef] [PubMed]

97. Karray, A.; Alonazi, M.; Jallouli, R.; Alanazi, H.; Ben Bacha, A. A Proteinaceous Alpha-Amylase Inhibitor from *Moringa oleifera* Leaf Extract: Purification, Characterization, and Insecticide Effects against *C. Maculates* Insect Larvae. *Molecules* **2022**, *27*, 4222. [CrossRef] [PubMed]

98. Ukwuani-Kwaja, A.; Sani, I.; Sylvester, M.N.N.; Kabir, A.O.; Abolaji, O.K.; Ukwuani-Kwaja, A.; Sani, I.; Sylvester, M.N.N. In-Vitro Antidiabetic Effect of *Ziziphus mucronata* Leave Extracts. *J. Drug Deliv. Ther.* **2021**, *11*, 9–13. [CrossRef]

99. Olaokun, O.O.; Manonga, S.A.; Zubair, M.S.; Maulana, S.; Mkolo, N.M. Molecular Docking and Molecular Dynamics Studies of Antidiabetic Phenolic Compound Isolated from Leaf Extract of *Englerophytum magalismontanum* (Sond.) T.D.Penn. *Molecules* **2022**, *27*, 3175. [CrossRef] [PubMed]

100. Yashoda, K.; Deegendra, K.; Bimala, S. Antioxidant, Ptp 1B Inhibition and A-Amylase Inhibition Property and Gc-Ms Analysis of Methanolic Leaves Extract of *Achyranthes aspera* and *Catharanthus roseus* of Nepal. *Int. J. Pharm. Pharm. Sci.* **2021**, *13*, 49–55. [CrossRef]

101. Irfan Dar, M.; Qureshi, M.I.; Zahiruddin, S.; Abass, S.; Jan, B.; Sultan, A.; Ahmad, S. In Silico Analysis of PTP1B Inhibitors and TLC-MS Bioautography-Based Identification of Free Radical Scavenging and α-Amylase Inhibitory Compounds from Heartwood Extract of *Pterocarpus marsupium*. *ACS Omega* **2022**, *7*, 46156–46173. [CrossRef]

102. Li, F.; Luo, T.; Hou, J.; Fei, T.; Zhang, J.; Wang, L. Natural α-Glucosidase and α-Amylase Inhibitors from Raspberry (*Rubus corchorifolius* L.) Leaf-Tea: Screening, Identification and Molecular Docking Analysis. *Lwt* **2023**, *181*, 114763. [CrossRef]

103. Yang, Y.; Zhang, P.; Huang, Z.; Zhao, Z. Phenolics from *Sterculia nobilis* Smith Pericarp By-Products Delay Carbohydrate Digestion by Uncompetitively Inhibiting α-Glucosidase and α-Amylase. *LWT* **2023**, *173*, 114339. [CrossRef]

104. Sakhr, K.; El Khatib, S. Physiochemical Properties and Medicinal, Nutritional and Industrial Applications of Lebanese Sumac (Syrian Sumac—*Rhus coriaria*): A Review. *Heliyon* **2020**, *6*, e03207. [CrossRef]

105. Pleşca-Manea, L.; Pârvu, A.E.; Pârvu, M.; Taǎmaş, M.; Buia, R.; Puia, M. Effects of *Melilotus officinalis* on Acute Inflammation. *Phyther. Res.* **2002**, *16*, 316–319. [CrossRef] [PubMed]

106. Burlando, B.; Verotta, L.; Cornara, L.; Bottini-Massa, E. *Herbal Principles in Cosmetics: Properties and Mechanisms of Action*; CRC Press: Boca Raton, FL, USA, 2010; ISBN 1439812144.

107. Bakhshayeshi, S.; Madani, S.; Hemmatabadi, M.; Heshmat, R.; Larijani, B. Effects of Semelil (ANGIPARS™) on Diabetic Peripheral Neuropathy: A Randomized, Double-Blind Placebo-Controlled Clinical Trial. *Daru* **2011**, *19*, 65–70.

108. Nithya, M.; Ragavendran, C.; Natarajan, D. Antibacterial and Free Radical Scavenging Activity of a Medicinal Plant Solanum Xanthocarpum. *Int. J. Food Prop.* **2018**, *21*, 313–327. [CrossRef]

109. Tekuri, S.K.; Pasupuleti, S.K.; Konidala, K.K.; Amuru, S.R.; Bassaiahgari, P.; Pabbaraju, N. Phytochemical and Pharmacological Activities of Solanum Surattense Burm. f.–A Review. *J. Appl. Pharm. Sci.* **2019**, *9*, 126–136. [CrossRef]

110. Pereira, A.P.A.; Lauretti, L.B.C.; Alvarenga, V.O.; Paulino, B.N.; Angolini, C.F.F.; Neri-Numa, I.A.; Orlando, E.A.; Pallone, J.A.L.; Sant'Ana, A.S.; Pastore, G.M. Evaluation of Fruta-Do-Lobo (Solanum Lycocarpum St. Hill) Starch on the Growth of Probiotic Strains. *Food Res. Int.* **2020**, *133*, 109187. [CrossRef] [PubMed]

111. Pereira, A.P.A.; Fernando Figueiredo Angolini, C.; de Souza-Sporkens, J.C.; da Silva, T.A.; Coutinho Franco de Oliveira, H.; Pastore, G.M. Brazilian Sunberry (*Solanum Oocarpum* Sendtn): Alkaloid Composition and Improvement of Mitochondrial Functionality and Insulin Secretion of INS-1E Cells. *Food Res. Int.* **2021**, *148*, 110589. [CrossRef]

112. Wu, L.; Liu, Y.; Qin, Y.; Wang, L.; Wu, Z. HPLC-ESI-QTOF-MS/MS Characterization, Antioxidant Activities and Inhibitory Ability of Digestive Enzymes with Molecular Docking Analysis of Various Parts of Raspberry (*Rubus ideaus* L.). *Antioxidants* **2019**, *8*, 274. [CrossRef]

113. Song, J.; Sun, P.; Wang, R.; Zhao, X. Gastroprotective Effects of Methanolic Extract of S Terculia Nobilis Smith Seeds in Reserpine-Induced Gastric Ulcer in Mice. *J. Food Biochem.* **2015**, *39*, 230–237. [CrossRef]

114. Zhang, Y.; Shen, R.; Mo, Y.; Li, Q.; Lin, W.; Yuan, G. Colletotrichum Siamense: A Novel Leaf Pathogen of *Sterculia nobilis* Smith Detected in China. *For. Pathol.* **2020**, *50*, e12575. [CrossRef]

115. Zhang, J.-J.; Li, Y.; Lin, S.-J.; Li, H.-B. Green Extraction of Natural Antioxidants from the *Sterculia nobilis* Fruit Waste and Analysis of Phenolic Profile. *Molecules* **2018**, *23*, 1059. [CrossRef]

116. Sharma, N.; Garg, V.; Paul, A. Antihyperglycemic, Antihyperlipidemic and Antioxidative Potential of *Prosopis cineraria* Bark. *Indian J. Clin. Biochem.* **2010**, *25*, 193–200. [CrossRef]

117. Kant, S. Pharmacological Evaluation of Antidiabetic and Antihyperlipidemic Activity of *Chenopodium album* Root Extract in Male Wistar Albino Rat Models. *Int. J. Green Pharm.* **2018**, *12*, 115–122. [CrossRef]

118. Odhav, B.; Kandasamy, T.; Khumalo, N.; Baijnath, H. Screening of African Traditional Vegetables for Their Alpha-Amylase Inhibitory Effect. *J. Med. Plants Res* **2010**, *4*, 1502–1507. [CrossRef]

119. Jordán, M.J.; Martínez, C.; Moñino, M.I.; Lax, V.; Quílez, M.; Sotomayor, J.A. Chemical Characterization of *Salvia lavandulifolia* Subsp. Vellerea in South-Eastern Spain. *Acta Hortic.* **2009**, 317–324. [CrossRef]

120. Zrira, S.; Menut, C.; Bessiere, J.M.; Elamrani, A.; Benjilali, B. A Study of the Essential Oil of *Salvia lavandulifolia* Vahl from Morocco. *J. Essent. Oil Bear. Plants* **2004**, *7*, 232–238. [CrossRef]

121. Zarzuelo, A.; Risco, S.; Gámez, M.J.; Jimenez, J.; Cámara, M.; Martinez, M.A. Hypoglycemic Action of Vahl. ssp.: A Contribution to Studies of the Mechanism of Action. *Life Sci.* **1990**, *47*, 909–915. [CrossRef]

122. Kabach, I.; Bouchmaa, N.; Zouaoui, Z.; Ennoury, A.; El Asri, S.; Laabar, A.; Oumeslakht, L.; Cacciola, F.; El Majdoub, Y.O.; Mondello, L.; et al. Phytochemical Profile and Antioxidant Capacity, α-Amylase and α-Glucosidase Inhibitory Activities of *Oxalis pes-caprae* Extracts in Alloxan-Induced Diabetic Mice. *Biomed. Pharmacother.* **2023**, *160*, 114393. [CrossRef] [PubMed]

123. Malik, A.; Sharif, A.; Zubair, H.M.; Akhtar, B.; Mobashar, A. In Vitro, In Silico, and In Vivo Studies of *Cardamine hirsuta* Linn as a Potential Antidiabetic Agent in a Rat Model. *ACS Omega* **2023**, *8*, 22623–22636. [CrossRef]

124. Wan, P.; Cai, B.; Chen, H.; Chen, D.; Zhao, X.; Yuan, H.; Huang, J.; Chen, X.; Luo, L.; Pan, J. Antidiabetic Effects of Protein Hydrolysates from *Trachinotus ovatus* and Identification and Screening of Peptides with α-Amylase and DPP-IV Inhibitory Activities. *Curr. Res. Food Sci.* **2023**, *6*, 100446. [CrossRef] [PubMed]

125. Naz, F.; Zahoor, M.; Ayaz, M.; Ashraf, M.; Nawaz, A.; Alotaibi, A. Anti-Diabetic Potentials of *Sorbaria tomentosa* Lindl. Rehder: Phytochemistry (GC-MS Analysis), α-Amylase, α-Glucosidase Inhibitory, in Vivo Hypoglycemic, and Biochemical Analysis. *Open Chem.* **2023**, *21*, 20220339. [CrossRef]

126. Hbika, A.; Daoudi, N.E.; Bouyanzer, A.; Bouhrim, M.; Mohti, H.; Loukili, E.H.; Mechchate, H.; Al-Salahi, R.; Nasr, F.A.; Bnouham, M.; et al. *Artemisia absinthium* L. Aqueous and Ethyl Acetate Extracts: Antioxidant Effect and Potential Activity In Vitro and In Vivo against Pancreatic α-Amylase and Intestinal α-Glucosidase. *Pharmaceutics* **2022**, *14*, 481. [CrossRef]

127. Bouknana, S.; Daoudi, N.E.; Bouhrim, M.; Ziyyat, A.; Legssyer, A.; Mekhfi, H.; Bnouham, M. *Ammodaucus leucotrichus* Coss. & Durieu: Antihyperglycemic Activity via the Inhibition of α-Amylase, α-Glucosidase, and Intestinal Glucose Absorption Activities and Its Chemical Composition. *J. Pharm. Pharmacogn. Res.* **2022**, *10*, 94–103. [CrossRef]

128. Zeng, A.; Yang, R.; Yu, S.; Zhao, W. A Novel Hypoglycemic Agent: Polysaccharides from Laver (*Porphyra* spp.). *Food Funct.* **2020**, *11*, 9048–9056. [CrossRef] [PubMed]

129. Xie, C.; Gao, W.; Li, X.; Luo, S.; Wu, D.; Chye, F.Y. Garlic (*Allium sativum* L.) Polysaccharide Ameliorates Type 2 Diabetes Mellitus (T2DM) via the Regulation of Hepatic Glycogen Metabolism. *NFS J.* **2023**, *31*, 19–27. [CrossRef]

130. Kashtoh, H.; Baek, K.-H. Recent Updates on Phytoconstituent Alpha-Glucosidase Inhibitors: An Approach towards the Treatment of Type Two Diabetes. *Plants* **2022**, *11*, 2722. [CrossRef] [PubMed]

131. Lam, T.; Tran, N.N.; Pham, L.D.; Lai, N.V.; Ngoc, B. Flavonoids as Dual- Target Inhibitors against α—Glucosidase and α -Amylase: A Systematic Review of in Vitro Studies. *Biol. Med. Chem.* **2023**, 1–41. [CrossRef]

132. Etxeberria, U.; De La Garza, A.L.; Campin, J.; Martnez, J.A.; Milagro, F.I. Antidiabetic Effects of Natural Plant Extracts via Inhibition of Carbohydrate Hydrolysis Enzymes with Emphasis on Pancreatic Alpha Amylase. *Expert Opin. Ther. Targets* **2012**, *16*, 269–297. [CrossRef]

133. Gong, L.; Feng, D.; Wang, T.; Ren, Y.; Liu, Y.; Wang, J. Inhibitors of α-Amylase and α-Glucosidase: Potential Linkage for Whole Cereal Foods on Prevention of Hyperglycemia. *Food Sci. Nutr.* **2020**, *8*, 6320–6337. [CrossRef]

134. Sivalingam, S.; Kandhasamy, S.; Chandrasekaran, S.; Vijayan, K.; Jacob, J.P.; Perumal, A.; Vijayakumar, S. A Flavone Derivative from Andrographis Echioides Leaf Extract Positively Alters the Molecular Targets of Insulin Signaling Pathway. *S. Afr. J. Bot.* **2022**, *146*, 760–770. [CrossRef]

135. Yang, Y.; Wang, Y.; Zeng, W.; Tian, J.; Zhao, X.; Han, J.; Huang, D.; Gu, D. A Strategy Based on Liquid-Liquid-Refining Extraction and High-Speed Counter-Current Chromatography for the Bioassay-Guided Separation of Active Compound from Taraxacum Mongolicum. *J. Chromatogr. A* **2020**, *1614*, 460727. [CrossRef]

136. Zhang, L.; Zeng, J.; Yuan, E.; Chen, J.; Zhang, Q.; Wang, Z.; Yin, Z. Extraction, Identification, and Starch-Digestion Inhibition of Phenolics from Euryale Ferox Seed Coat. *J. Sci. Food Agric.* **2023**, *103*, 3437–3446. [CrossRef]

137. Sahnoun, M.; Bejar, S.; Daoud, L.; Ayadi, L.; Brini, F.; Saibi, W. Effect of *Agave americana* L. on the Human, and Aspergillus Oryzae S2 α-Amylase Inhibitions. *Nat. Prod. Res.* **2019**, *33*, 755–758. [CrossRef] [PubMed]

138. Wu, S.; Tian, L. A New Flavone Glucoside Together with Known Ellagitannins and Flavones with Anti-Diabetic and Anti-Obesity Activities from the Flowers of Pomegranate (*Punica granatum*). *Nat. Prod. Res.* **2019**, *33*, 252–257. [CrossRef] [PubMed]

139. Mohamed, G.A.; Omar, A.M.; El-Araby, M.E.; Mass, S.; Ibrahim, S.R.M. Assessments of Alpha-Amylase Inhibitory Potential of Tagetes Flavonoids through In Vitro, Molecular Docking, and Molecular Dynamics Simulation Studies. *Int. J. Mol. Sci.* **2023**, *24*, 10195. [CrossRef] [PubMed]

140. Soltani, S.; Koubaa, I.; Dhouib, I.; Khemakhem, B.; Marchand, P.; Allouche, N. New Specific A—Glucosidase Inhibitor Flavonoid from Thymelaea Tartonraira Leaves: Structure Elucidation, Biological and Molecular Docking Studies. *Chem. Biodivers.* **2023**, *20*, e202200944. [CrossRef]

141. Luyen, N.T.; Binh, P.T.; Tham, P.T.; Hung, T.M.; Dang, N.H.; Dat, N.T.; Thao, N.P. Wedtrilosides A and B, Two New Diterpenoid Glycosides from the Leaves of *Wedelia trilobata* (L.) Hitchc. with α-Amylase and α-Glucosidase Inhibitory Activities. *Bioorg. Chem.* **2019**, *85*, 319–324. [CrossRef]

142. Etsassala, N.G.E.R.; Badmus, J.A.; Marnewick, J.L.; Iwuoha, E.I.; Nchu, F.; Hussein, A.A. Alpha-Glucosidase and Alpha-Amylase Inhibitory Activities, Molecular Docking, and Antioxidant Capacities of Salvia Aurita Constituents. *Antioxidants* **2020**, *9*, 1149. [CrossRef]

143. Mohammed, A.; Victoria Awolola, G.; Ibrahim, M.A.; Anthony Koorbanally, N.; Islam, M.S. Oleanolic Acid as a Potential Antidiabetic Component of *Xylopia Aethiopica* (Dunal) A. Rich. (Annonaceae) Fruit: Bioassay Guided Isolation and Molecular Docking Studies. *Nat. Prod. Res.* **2021**, *35*, 788–791. [CrossRef]

144. Verma, A.; Pathak, P.; Rimac, H.; Khalilullah, H.; Kumar, V.; Grishina, M.; Potemkin, V.; Ahmed, B. A Triterpene Glochidon from Phyllanthus Debilis: Isolation, Computational Studies, and Antidiabetic Activity Evaluation. *Biocatal. Agric. Biotechnol.* **2021**, *36*, 102138. [CrossRef]

145. Monzón Daza, G.; Meneses Macías, C.; Forero, A.M.; Rodríguez, J.; Aragón, M.; Jiménez, C.; Ramos, F.A.; Castellanos, L. Identification of α-Amylase and α-Glucosidase Inhibitors and Ligularoside A, a New Triterpenoid Saponin from *Passiflora Ligularis* Juss (*Sweet granadilla*) Leaves, by a Nuclear Magnetic Resonance-Based Metabolomic Study. *J. Agric. Food Chem.* **2021**, *69*, 2919–2931. [CrossRef]

146. Uddin, M.J.; Russo, D.; Haque, M.A.; Çiçek, S.S.; Sönnichsen, F.D.; Milella, L.; Zidorn, C. Bioactive Abietane-Type Diterpenoid Glycosides from Leaves of *Clerodendrum infortunatum* (*Lamiaceae*). *Molecules* **2021**, *26*, 4121. [CrossRef] [PubMed]

147. Wu, M.; Li, W.; Zhang, Y.; Shi, L.; Xu, Z.; Xia, W.; Zhang, W. Structure Characteristics, Hypoglycemic and Immunomodulatory Activities of Pectic Polysaccharides from Rosa Setate x Rosa Rugosa Waste. *Carbohydr. Polym.* **2021**, *253*, 117190. [CrossRef] [PubMed]

148. Gong, P.; Guo, Y.; Chen, X.; Cui, D.; Wang, M.; Yang, W.; Chen, F. Structural Characteristics, Antioxidant and Hypoglycemic Activities of Polysaccharide from Siraitia Grosvenorii. *Molecules* **2022**, *27*, 4192. [CrossRef]

149. Quan, N.; Wang, Y.D.; Li, G.R.; Liu, Z.Q.; Feng, J.; Qiao, C.L.; Zhang, H.F. Ultrasound–Microwave Combined Extraction of Novel Polysaccharide Fractions from Lycium Barbarum Leaves and Their In Vitro Hypoglycemic and Antioxidant Activities. *Molecules* **2023**, *28*, 3880. [CrossRef]

150. Jiang, X.; Yang, T.; Li, Y.; Liu, S.; Liu, Y.; Chen, D.; Qin, W.; Zhang, Q.; Lin, D.; Liu, Y.; et al. Ultrasound-Assisted Extraction of Tamarind Xyloglucan: An Effective Approach to Reduce the Viscosity and Improve the α-Amylase Inhibition of Xyloglucan. *J. Sci. Food Agric.* **2022**, *103*, 4047–4057. [CrossRef]

151. Chen, Y.; Chen, Z.; Guo, Q.; Gao, X.; Ma, Q.; Xue, Z.; Ferri, N.; Zhang, M.; Chen, H. Identification of Ellagitannins in the Unripe Fruit of Rubus Chingii Hu and Evaluation of Its Potential Antidiabetic Activity. *J. Agric. Food Chem.* **2019**, *67*, 7025–7039. [CrossRef]

152. Cuc, N.T.; Cuong, N.T.; Anh, L.T.; Yen, D.T.H.; Tai, B.H.; Thu Trang, D.; Yen, P.H.; Van Kiem, P.; Nam, N.H.; Van Minh, C.; et al. Dihydrostilbene Glycosides from Camellia Sasanqua and Their α-Glucosidase and α-Amylase Inhibitory Activities. *Nat. Prod. Res.* **2021**, *35*, 4025–4031. [CrossRef] [PubMed]

153. Wang, M.; Chen, J.; Ye, X.; Liu, D. In Vitro Inhibitory Effects of Chinese Bayberry (*Myrica rubra* Sieb. et Zucc.) Leaves Proanthocyanidins on Pancreatic α-Amylase and Their Interaction. *Bioorg. Chem.* **2020**, *101*, 104029. [CrossRef]

154. Dandekar, P.D.; Kotmale, A.S.; Chavan, S.R.; Kadlag, P.P.; Sawant, S.V.; Dhavale, D.D.; Ravikumar, A. Insights into the Inhibition Mechanism of Human Pancreatic α-Amylase, a Type 2 Diabetes Target, by Dehydrodieugenol B Isolated from Ocimum Tenuiflorum. *ACS Omega* **2021**, *6*, 1780–1786. [CrossRef] [PubMed]

155. Sampath, S.N.T.I.; Jayasinghe, S.; Attanayake, A.P.; Karunaratne, V.; Yaddehige, M.L.; Watkins, D.L. A New Dimeric Carbazole Alkaloid from *Murraya koenigii* (L.) Leaves with α-Amylase and α-Glucosidase Inhibitory Activities. *Phytochem. Lett.* **2022**, *52*, 87–91. [CrossRef]

156. Naik, S.; Deora, N.; Pal, S.K.; Ahmed, M.Z.; Alqahtani, A.S.; Shukla, P.K.; Venkatraman, K.; Kumar, S. Purification, Biochemical Characterization, and DPP-IV and α-Amylase Inhibitory Activity of Berberine from Cardiospermum Halicacabum. *J. Mol. Recognit.* **2022**, *35*, e2983. [CrossRef]

157. Thuy, N.T.K.; Phuong, P.T.; Hien, N.T.T.; Trang, D.T.; Van Huan, N.; Anh, P.T.L.; Tai, B.H.; Nhiem, N.X.; Hung, N.T.; Kiem, P. Van Pregnane Glycosides from the Leaves of Dregea Volubilis and Their α-Glucosidase and α-Amylase Inhibitory Activities. *Nat. Prod. Res.* **2021**, *35*, 3931–3938. [CrossRef] [PubMed]

158. Van Kiem, P.; Yen, D.T.H.; Van Hung, N.; Nhiem, N.X.; Tai, B.H.; Trang, D.T.; Yen, P.H.; Ngoc, T.M.; Van Minh, C.; Park, S.; et al. Five New Pregnane Glycosides from Gymnema Sylvestre and Their α-Glucosidase and α-Amylase Inhibitory Activities. *Molecules* **2020**, *25*, 2525. [CrossRef] [PubMed]

159. Yang, L.; Zhang, D.; Li, J.-B.; Zhang, X.; Zhou, N.; Zhang, W.-Y.; Lu, H. Prenylated Xanthones with α-Glucosidase and α-Amylase Inhibitory Effects from the Pericarp of Garcinia Mangostana. *J. Asian Nat. Prod. Res.* **2022**, *24*, 624–633. [CrossRef]

160. Ibrahim, S.R.M.; Mohamed, G.A.; Khayat, M.T.A.; Ahmed, S.; Abo-Haded, H. Garcixanthone D, a New Xanthone, and Other Xanthone Derivatives from Garcinia Mangostana Pericarps: Their α-Amylase Inhibitory Potential and Molecular Docking Studies. *Starch/Staerke* **2019**, *71*, 1800354. [CrossRef]

161. Kawee-Ai, A.; Kim, A.T.; Kim, S.M. Inhibitory Activities of Microalgal Fucoxanthin against α-Amylase, α-Glucosidase, and Glucose Oxidase in 3T3-L1 Cells Linked to Type 2 Diabetes. *J. Oceanol. Limnol.* **2019**, *37*, 928–937. [CrossRef]

162. Makinde, E.A.; Ovatlarnporn, C.; Sontimuang, C.; Herbette, G.; Olatunji, O.J. Chemical Constituents from the Aerial Part of *Tiliacora Triandra* (Colebr.) Diels and Their α-Glucosidase and α-Amylase Inhibitory Activity. *Nat. Prod. Commun.* **2020**, *15*. [CrossRef]

163. Ravi, L.; Girish, S.; D'Souza, S.R.; Anirudh Sreenivas, B.K.; Shree Kumari, G.R.; Archana, O.; Ajith Kumar, K.; Manjunathan, R. β-Sitosterol, a Phytocompound from *Parthenium hysterophorus*, Reveals Anti-Diabetic Properties through α-Amylase Inhibition: An i n-Silico and in-Vitro Analysis. *J. Biomol. Struct. Dyn.* **2023**, 1–12. [CrossRef]

164. Zhu, J.; Chen, C.; Zhang, B.; Huang, Q. The Inhibitory Effects of Flavonoids on α-Amylase and α-Glucosidase. *Crit. Rev. Food Sci. Nutr.* **2020**, *60*, 695–708. [CrossRef]

165. Maleki, S.J.; Crespo, J.F.; Cabanillas, B. Anti-Inflammatory Effects of Flavonoids. *Food Chem.* **2019**, *299*, 125124. [CrossRef] [PubMed]

166. Górniak, I.; Bartoszewski, R.; Króliczewski, J. Comprehensive Review of Antimicrobial Activities of Plant Flavonoids. *Phytochem. Rev.* **2019**, *18*, 241–272. [CrossRef]

167. Proença, C.; Ribeiro, D.; Freitas, M.; Fernandes, E. Flavonoids as Potential Agents in the Management of Type 2 Diabetes through the Modulation of α-Amylase and α-Glucosidase Activity: A Review. *Crit. Rev. Food Sci. Nutr.* **2022**, *62*, 3137–3207. [CrossRef]

168. Williams, L.K.; Li, C.; Withers, S.G.; Brayer, G.D. Order and Disorder: Differential Structural Impacts of Myricetin and Ethyl Caffeate on Human Amylase, an Antidiabetic Target. *J. Med. Chem.* **2012**, *55*, 10177–10186. [CrossRef]

169. Ajikumar, P.K.; Tyo, K.; Carlsen, S.; Mucha, O.; Phon, T.H.; Stephanopoulos, G. Terpenoids: Opportunities for Biosynthesis of Natural Product Drugs Using Engineered Microorganisms. *Mol. Pharm.* **2008**, *5*, 167–190. [CrossRef] [PubMed]

170. Masyita, A.; Mustika Sari, R.; Dwi Astuti, A.; Yasir, B.; Rahma Rumata, N.; Emran, T.B.; Nainu, F.; Simal-Gandara, J. Terpenes and Terpenoids as Main Bioactive Compounds of Essential Oils, Their Roles in Human Health and Potential Application as Natural Food Preservatives. *Food Chem. X* **2022**, *13*, 100217. [CrossRef] [PubMed]

171. Teoh, S.L.; Das, S. Phytochemicals and Their Effective Role in the Treatment of Diabetes Mellitus: A Short Review. *Phytochem. Rev.* **2018**, *17*, 1111–1128. [CrossRef]

172. Etsassala, N.G.E.R.; Badmus, J.A.; Waryo, T.T.; Marnewick, J.L.; Cupido, C.N.; Hussein, A.A.; Iwuoha, E.I. Alpha-Glucosidase and Alpha-Amylase Inhibitory Activities of Novel Abietane Diterpenes from Salvia Africana-Lutea. *Antioxidants* **2019**, *8*, 421. [CrossRef]

173. He, L.Y.; Li, Y.; Niu, S.Q.; Bai, J.; Liu, S.J.; Guo, J.L. Polysaccharides from Natural Resource: Ameliorate Type 2 Diabetes Mellitus via Regulation of Oxidative Stress Network. *Front. Pharmacol.* **2023**, *14*, 1184572. [CrossRef]

174. Wang, P.-C.; Zhao, S.; Yang, B.-Y.; Wang, Q.-H.; Kuang, H.-X. Anti-Diabetic Polysaccharides from Natural Sources: A Review. *Carbohydr. Polym.* **2016**, *148*, 86–97. [CrossRef] [PubMed]

175. Ganesan, K.; Xu, B. Anti-Diabetic Effects and Mechanisms of Dietary Polysaccharides. *Molecules* **2019**, *24*, 2556. [CrossRef] [PubMed]

176. Wu, J.; Shi, S.; Wang, H.; Wang, S. Mechanisms Underlying the Effect of Polysaccharides in the Treatment of Type 2 Diabetes: A Review. *Carbohydr. Polym.* **2016**, *144*, 474–494. [CrossRef] [PubMed]

177. Xiao, M.; Jia, X.; Wang, N.; Kang, J.; Hu, X.; Goff, H.D.; Cui, S.W.; Ding, H.; Guo, Q. Therapeutic Potential of Non-Starch Polysaccharides on Type 2 Diabetes: From Hypoglycemic Mechanism to Clinical Trials. *Crit. Rev. Food Sci. Nutr.* **2022**, 1–34. [CrossRef]

178. Tanna, B.; Mishra, A. Nutraceutical Potential of Seaweed Polysaccharides: Structure, Bioactivity, Safety, and Toxicity. *Compr. Rev. Food Sci. Food Saf.* **2019**, *18*, 817–831. [CrossRef]

179. Sheng, K.; Wang, C.; Chen, B.; Kang, M.; Wang, M.; Liu, K.; Wang, M. Recent Advances in Polysaccharides from Lentinus Edodes (Berk.): Isolation, Structures and Bioactivities. *Food Chem.* **2021**, *358*, 129883. [CrossRef]

180. Cao, C.; Li, C.; Chen, Q.; Huang, Q.; Pérez, M.E.M.; Fu, X. Physicochemical Characterization, Potential Antioxidant and Hypoglycemic Activity of Polysaccharide from Sargassum Pallidum. *Int. J. Biol. Macromol.* **2019**, *139*, 1009–1017. [CrossRef] [PubMed]

181. Tan, M.; Zhao, Q.; Zhao, B. Physicochemical Properties, Structural Characterization and Biological Activities of Polysaccharides from Quinoa (*Chenopodium quinoa* Willd.) Seeds. *Int. J. Biol. Macromol.* **2021**, *193*, 1635–1644. [CrossRef]

182. Li, Y.M.; Zhong, R.F.; Chen, J.; Luo, Z.G. Structural Characterization, Anticancer, Hypoglycemia and Immune Activities of Polysaccharides from Russula Virescens. *Int. J. Biol. Macromol.* **2021**, *184*, 380–392. [CrossRef]

183. Bodoira, R.; Maestri, D. Phenolic Compounds from Nuts: Extraction, Chemical Profiles, and Bioactivity. *J. Agric. Food Chem.* **2020**, *68*, 927–942. [CrossRef] [PubMed]

184. Kumar, N.; Goel, N. Phenolic Acids: Natural Versatile Molecules with Promising Therapeutic Applications. *Biotechnol. Reports* **2019**, *24*, e00370. [CrossRef]

185. Vinayagam, R.; Jayachandran, M.; Xu, B. Antidiabetic Effects of Simple Phenolic Acids: A Comprehensive Review. *Phyther. Res.* **2016**, *30*, 184–199. [CrossRef]

186. Marsh, K.J.; Wallis, I.R.; Kulheim, C.; Clark, R.; Nicolle, D.; Foley, W.J.; Salminen, J.P. New Approaches to Tannin Analysis of Leaves Can Be Used to Explain in Vitro Biological Activities Associated with Herbivore Defence. *New Phytol.* **2020**, *225*, 488–498. [CrossRef] [PubMed]

187. Ajebli, M.; Eddouks, M. The Promising Role of Plant Tannins as Bioactive Antidiabetic Agents. *Curr. Med. Chem.* **2018**, *26*, 4852–4884. [CrossRef] [PubMed]