Natural Products as α-Amylase and α-Glucosidase Inhibitors and their Hypoglycaemic Potential in the Treatment of Diabetes: An Update

R. Tundis*, M.R. Loizzo and F. Menichini

Department of Pharmaceutical Sciences, Faculty of Pharmacy, Nutrition and Health Sciences, University of Calabria, 87036-I Rende (CS), Italy

Abstract: The inhibition of α-glucosidase and α-amylase, enzymes involved in the digestion of carbohydrates, can significantly reduce the post-prandial increase of blood glucose and therefore can be an important strategy in the management of blood glucose level in type 2 diabetic and borderline patients. Currently, there is renewed interest in plant-based medicines and functional foods modulating physiological effects in the prevention and cure of diabetes and obesity.

The plant kingdom is a wide field to search for natural effective oral hypoglycaemic agents that have slight or no side effects. More than ca. 1200 plant species have been recorded to be used empirically worldwide for their alleged hypoglycaemic activity. Therefore, natural α-glucosidase and α-amylase inhibitors from plant sources offer an attractive strategy for the control of hyperglycaemia. This article reviews recent data on plant extracts and isolated natural compounds that are being tested for their hypoglycaemic activity, highlights ongoing research and considers the future perspectives.

Keywords: Diabetes, Post-prandial Hyperglycaemia, α-Glucosidase, α-Amylase, Extract, Natural compounds.

INTRODUCTION

Diabetes mellitus affects about 5% of the global population and its management without any side effects is still a challenge to the medical system [1,2]. Type 2 diabetes is a heterogeneous disease resulting from a dynamic interaction between defects in insulin secretion and insulin action. Such a deficiency results in increased concentrations of blood glucose, which in turn damage many of the body's systems, in particular the blood vessels. These disorders included retinopathy, nephropathy, neuropathy, and angiopathy. The natural history of the disease is characterized by a progressive exhaustion of β cells. Patients with type 2 diabetes are insulin-resistant and often have a metabolic syndrome, a multifactorial intervention including aggressive treatment of arterial hypertension and dyslipidaemia [3]. As most subjects are over weighted or obese, the initial treatment is optimization of the meal plan and enhancement of physical activity in order to obtain sustained weight reduction. In case of failure of life-style changes, various oral hypoglycaemic agents may be used. The aim of antidiabetic therapy is to reach normoglycaemia and to reduce insulin resistance, thereby improving metabolic control with the intention to prevent diabetic late complications. These may be inhibited or lowered by maintaining blood glucose values close to normal. Some are targeting defective insulin secretion (sulphonylureas, glinides) while others are targeting insulin resistance (metformin, thiazolidinediones). One therapeutic approach for treating in the early stage diabetes is to decrease post-prandial hyperglycaemia. This is done by retarding the absorption of glucose through the inhibition of the carbohydrate-hydrolyzing enzymes, α-amylase and α-glucosidase, in the digestive tract. Consequently, inhibitors of these enzymes determine a reduction in the rate of glucose absorption and consequently blunting the post-prandial plasma glucose rise [4,5].

These drugs also have certain adverse effects like causing hypoglycaemia at higher doses, liver problems, lactic acidosis and diarrhoea. Apart from currently available therapeutic options, many herbal medicines have been recommended for the treatment of diabetes. Traditional plant medicines are used throughout the world for a range of diabetic presentations. Herbal drugs are prescribed widely because of their effectiveness, less side effects and relatively low cost [6]. Therefore, investigation on such agents from traditional medicinal plants has become more important. Recently, McDougall and Stewart [7] reviewed the effects of polyphenols from berries on digestive enzymes, Matsui *et al.* [8] reported the potential inhibitory effect on α-glucosidase of anthocyanins, caffeic acid and caffeoylquinic acid analogs, and Mukherjee *et al.* [9] described the chemistry, activity and traditional use as antidiabetic of constituents isolated from different Indian plants. The present review article summarizes and highlights the recent developments in plants and plant derived natural products as α-amylase and α-glucosidase inhibitors. The mechanism of action and the structure activity relationships (SARs) were also discussed where it is possible.

ENZYMES

α-Amylase

α-Amylase (1,4-α-D-glucan-glucanohydrolase, EC 3.2.1.1) catalyzes the hydrolysis of α-1,4-glucan bonds in starch, maltodextrins and maltooligosaccharides. This enzyme is

*Address correspondence to this author at the Department of Pharmaceutical Sciences, Faculty of Pharmacy, Nutrition and Health Sciences, University of Calabria, Itlay; Tel: +39 984 493169; Fax: +39 984 493298;
E-mail: tundis@unical.it

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present in animals, plants, bacteria and fungi [10]. In humans the digestion of starch involves several stages. Initially, partial digestion by the salivary amylase results in the degradation of the polymeric substrate into shorter oligomers [11]. Once this partially digested material reaches the gut, it is then extensively hydrolyzed into smaller oligosaccharides by the α-amylase isozyme synthesized in the pancreas and excreted into the lumen. The resultant mixture of oligosaccharides passes through the mucous layer of the brush border membrane, where additional α-glucosidases degrade it to glucose, which then enters the blood stream by means of a specific transport system.

Human pancreatic α-amylase belongs to family 13 of the sequence-related groupings assembled for glycosidases and glycosyl transferases [12]. Despite low overall amino acid sequence homology within this family, short regions of highly conserved residues are present and structural studies have demonstrated that members of this family indeed have similar 3-dimensional structures [13]. These isozymes are encoded on chromosome 1 as part of a multigene family that is regulated so that the different isozymes are expressed solely in either the salivary glands or the pancreas [14]. The former amylase encoded by the *amy* 1 gene is expressed in the salivary, mammary and lachrymal glands, while the pancreatic amylase isozyme encoded by the *amy* 2 gene is expressed only in the pancreas. It contains three structural domains, A, B and C. The $(\beta/\alpha)_8$ barrel A domain (residues 1-99 and 169-404) contains the active site triad Asp197, Glu233 and Asp300. The B domain is a large loop (100-168) which occurs between the third β-strand and the α-helix of the barrel domain. A calcium ion facilitates the binding of the B domain to the A domain. The C domain (405-496) differs from the two latter domains, since it is a β-stranded domain [13, 15-18].

In common with other family 13 enzymes, human pancreatic α-amylase is believed to catalyze the hydrolysis of starch *via* a double displacement mechanism involving the formation and hydrolysis of a covalent α-glycosyl enzyme intermediate. Formation of this intermediate involves attack at the sugar anomeric centre by a nucleophilic amino acid, most likely Asp197 by analogy with other family 13 enzyme sequences. This is assisted by general-acid catalysis provided by one or both of the other two active site carboxylic acids (Glu233 or Asp300). The covalent glycosyl enzyme intermediate then undergoes general-base-catalyzed hydrolysis *via* attack of water at the anomeric centre, again assisted by one or both of the carboxyl groups of Glu233 or Asp300. This proposed mechanism is believed to proceed *via* oxocarbenium ion-like transition states [19].

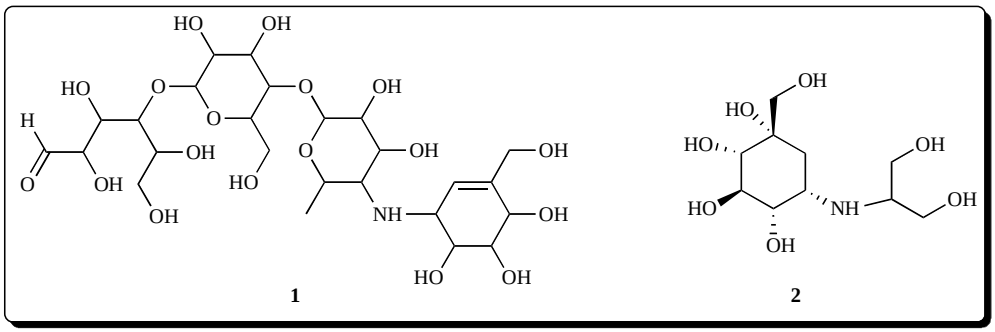
α-Glucosidase

α-Glucosidase (EC 3.2.1.20) catalyzes the hydrolytic reaction to liberate α-glucose from the non-reducing end of the substrate [20-24]. The enzyme also shows the transferring reaction and the condensation as well as the hydration of D-glucal [22, 25, 26]. α-Glucosidases are mainly classified into two groups, GH-family 13 and 31, based on the sequence homology [27-29]. Their origins are also different [20,22]. Plant, animal, mold, bacteria and human α-glucosidases as well as α-glucan lyase (EC 4.2.2.13) [30] and α-xylosidase [31] are members of GH-family 31 [23]. These enzymes were membrane-bound enzymes located at the epithelium of the small intestine [32], and the key enzymes of carbohydrate digestion [33]. Recently, Saqib *et al*. [34] construct the three-dimensional model of human α-glucosidase and investigate the binding interactions with competitive inhibitor acarbose (**1**). Besides the conserved catalytic GH-31 domain (residues 334-779), a variable loop originating from the *N*-terminal domain (residues 271-288) contribute towards the architecture of substrate binding site. Secondary structure elements consist of 10 alpha helices and 28 small beta sheets with intermittent loop regions. Human α-glucosidase active site is a pocket formed mainly by the GH31 domain residues specifically Asp398, Asp587, His645, and Arg571. Residues Trp472 and Phe518 come into proximity to the opening of the active site and contribute towards the architecture of the substrate binding site. Additional residues lining the sugar-binding site include Asp511, Trp370, Ile435, Trp509, and Met512. The study of virtual screening between human α-glucosidase and acarbose evidenced that the residues Asp547, Asp511, Asp398, Arg571 and His645 are important for strong hydrogen binding interaction.

TREATMENT OF HYPERGLYCEMIA

The inhibition of α-glucosidase and α-amylase enzymes can significantly reduce the post-prandial increase of blood glucose after a mixed carbohydrate diet and therefore can be an important strategy in the management of type 2 diabetic patients and borderline patients [35-37]. Therefore, new agents, which control post-prandial hyperglycaemia, have been developed. Among them acarbose (**1**) and voglibose (**2**) have received considerable attention in the past decades [38-42].

Acarbose is a natural product produced by *Actinoplanes* sp. fermentation [43]. It is a pseudotetrasaccharide with an



unsaturated cyclitol [2,3,4-trihydroxy-5-(hydroxymethyl)-5,6-cyclohexene in a D-*gluco* configuration] attached to the nitrogen of 4-amino-4,6-dideoxy-D-glucopyranose, which is linked α-(1→4) to maltose. Some acarbose analogues, that have maltodextrin residues attached to the reducing-end and/or to the nonreducing-end of acarbose, were produced by *Actinoplanes* sp. fermentation. These analogues showed inhibitory activity against α-amylase and sucrase that was altered by the number of D-glucose units in the maltodextrins at the two ends [44]. Various other kinds of acarbose analogues have been obtained by the modification of the maltose unit at the reducing-end, using the transglycosylation reaction of *Bacillus stearothermophilus* maltogenic amylase (BSMA) with acarbose and several carbohydrate acceptors [45-47]. It was found that the removal of one D-glucose residue from the reducing end of acarbose, to give acarviosine-glucose, inhibited yeast a-glucosidase 430-times better than acarbose. The replacement of the maltose unit by isomaltose gave an inhibitor that inhibited porcine pancreatic α-amylase 15.2-times better than acarbose. It was also reported [48] the synthesis of acarbose analogues with maltohexaose, maltododecaose, and maltooctadecaose attached to the C-4-hydroxyl group of the nonreducingend of acarbose by the reaction of cyclomaltodextrin glucanyltransferase with cyclomaltohexaose and acarbose.

Apart from currently available therapeutic options, many herbal medicines have been recommended for the treatment of diabetes. Traditional plant medicines are used throughout the world for a range of diabetic presentations. The relatively reduced cases of adverse reaction to plant preparations, as compared to modern conventional pharmaceuticals [49-52], coupled with their reduced cost, is encouraging both the consuming public and national health care institutions to consider natural medicinal products as alternatives to synthetic drugs [53]. Therefore, the investigation on such agents from traditional medicinal plants has become more important [54].

EXTRACTS

The hypoglycaemic activity of *Schkuhria pinnata*, *Pteronia divaricata*, *Euclea undulata* var. *myrtina*, and *Elaeodendron transvaalense*, traditionally used for the treatment of diabetes in South African, was investigated [55]. *P. divaricata* acetone extract inhibited α-glucosidase with an IC_{50} value of 31.22 μg/ml. In the α-amylase assay, *E. undulata* and *E. transvaalense* acetone extract inhibited the enzyme with IC_{50} values of 2.80 and 1.12 μg/ml, respectively. Acetone extracts of *S. pinnata* showed no inhibition.

The chloroform, methanol and aqueous extracts prepared from either leaves or seeds of six ethno-botanically known plants having antidiabetic property, namely *Azadirachta indica*, *Murraya koenigii*, *Ocimum tenuflorum*, *Syzygium cumini*, *Linum usitatissimum* and *Bougainvillea spectabilis*, were tested for their ability to inhibit glucosidase activity [56]. The chloroform extract of *O. tenuflorum*, *B. spectabilis*, *M. koenigii*, and *S. cumini* showed significant α-amylase inhibitory property. Plants extracts were further tested against murine pancreatic, liver and small intestinal crude enzyme preparations for glucosidase inhibitory activity. The chloroform extract of *M. koenigii* showed significant inhibition (IC_{50} ranging from 1.06 μg/ml to 2.68 μg/ml) with porcine pancreatic α-amylase as well as murine pancreatic and intestinal glucosidases, respectively. Interestingly, the phenolic content of this extract was very low, so the inhibitory activity may be because of specific inhibitory compounds. The methanolic extract showed inhibition (IC_{50} value of 1.96 μg/ml) only with murine intestinal glucosidase. Similarly, *O. tenuflorum* inhibited α-amylase. The three extracts of *O. tenuflorum* showed inhibitory activity against porcine α-amylase, murine pancreatic and liver glucosidases. The chloroform extract exhibited the highest inhibitory activity with murine pancreatic glucosidases (IC_{50} value of 1.76 μg/ml). The inhibitory activity of aqueous extract was observed with porcine α-amylase and murine liver glucosidases, respectively (IC_{50} values of 1.55 and 9.86 μg/ml). A good inhibitory activity was obtained with the chloroform extract of both *S. cumini* and *B. spectabilis* against porcine α-amylase, murine pancreatic and murine intestinal glucosidases. Both methanolic (IC_{50} values of 2.60 and 1.80 μg/ml) and aqueous extract of *A. indica* (IC_{50} values of 3.17 and 6.21 μg/ml) showed inhibition significantly more than acarbose against murine liver and intestinal glucosidases, respectively. *L. usitatissimum* is known to possess plasma triglycerides and cholesterol lowering properties. This plant being a dietary component is also known to have hypolipidemic effect [57]. The aqueous and methanolic extract significantly inhibited murine pancreatic glucosidases with IC_{50} values of 3.21 μg/ml and 18.62 μg/ml, respectively.

Recently, the methanol, *n*-hexane and chloroform extracts of *Calamintha origanifolia, Satureja thymbra, Prangos asperula, Sideritis perfoliata, Asperula glomerata, Hyssopus officinalis, Erythraea centaurium, Marrubium radiatum* and *Salvia acetabulosa*, collected in Lebanon, were analysed for their ability to inhibit both carbohydrate-hydrolyzing enzymes Fig. (**1-3**) [58]. M. radiatum methanol extract exerted the highest inhibitory activity against both α-amylase and α-glucosidase with IC_{50} values of 61.1 and 68.8 μg/ml, respectively. Interestingly, n-hexane and chloroform extracts obtained from the same plant did not exhibit significant activity on α-amylase, while a good activity was found with α-glucosidase (IC_{50} of 114.7 and 128.5 μg/ml, respectively). Novaes *et al.* [59] showed a significant *in vivo* hypoglycaemic effect of M. vulgare, used in Brazilian and Mexican traditional medicine. A recent clinical trial on patients with type 2 non controlled diabetes mellitus demonstrated that M. vulgare leaf extract reduced the plasma glucose level by 0.64%, providing some support for its reported use in type 2 diabetes [60]. S. acetabulosa methanol extract showed IC_{50} values of 76.9 and 91.2 μg/ml for α-glucosidase and α-amylase, respectively. The activity of S. acetabulosa n-hexane extract on both enzymes was weaker, with an IC_{50} values of 205.5 and 212.0 μg/ml for α-amylase and α-glucosidase, respectively. The use of chloroform as solvent drastically reduced the inhibitory effect on α-amylase, but had little effect on the ability of S. acetabulosa to inhibit α-glucosidase. The n-hexane and chloroform extracts of the C. origanifolia exerted the highest α-glucosidase inhibition activity (IC_{50} of 63.5 and 102.1 μg/ml, respectively). Both extracts also inhibited α-amylase with IC_{50} values of 94.1 and 91.6 μg/ml, respectively. E. centaurium chloroform extract exhibited a good inhibitory activity on both enzymes with an IC_{50} of 64.9 and 74.9 μg/ml for α-amylase and α-

glucosidase, respectively. At the same time methanol and n-hexane extracts of E. centaurium exhibited no inhibition. H. officinalis extracts were active only on the α-glucosidase enzyme, with IC_{50} values ranging from 127.3 to 908.4 μg/ml. A. glomerata methanol and n-hexane extracts inhibited α-glucosidase (IC_{50} 128.5 and 190.5 μg/ml, respectively) with weaker effects against α-amylase (IC_{50} of 209.7 and 330.9 μg/ml for methanol and n-hexane extracts respectively). S. perfoliata gave only a weak inhibition against α-glucosidase. The activity of S. thymbra chloroform extract (IC_{50} of 351.6 and 289.8 μg/ml against α-amylase and α-glucosidase, respectively) is noteworthy.

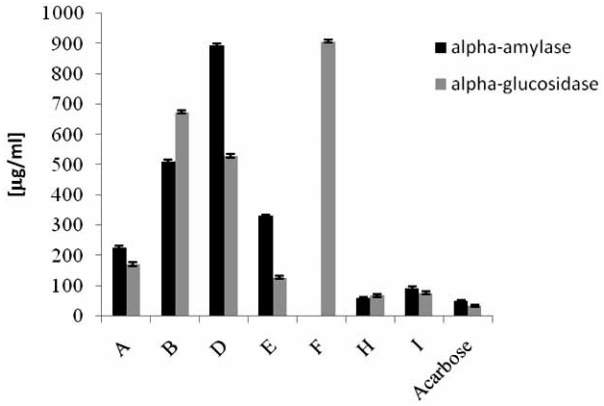


Fig. (1). α-Amylase and α-glucosidase inhibitory activity of methanol extracts from Lebanese traditional medicinal plants (IC_{50} μg/ml). *C. origanifolia* (**A**), *S. thymbra* (**B**), *P. asperula* (**C**), *S. perfoliata* (**D**), *A. glomerata* (**E**), *H. officinalis* (**F**), *E. centaurium* (**G**), *M. radiatum* (**H**), *S. acetabulosa* (**I**). IC_{50} values are mean ± S.D. (n = 3).

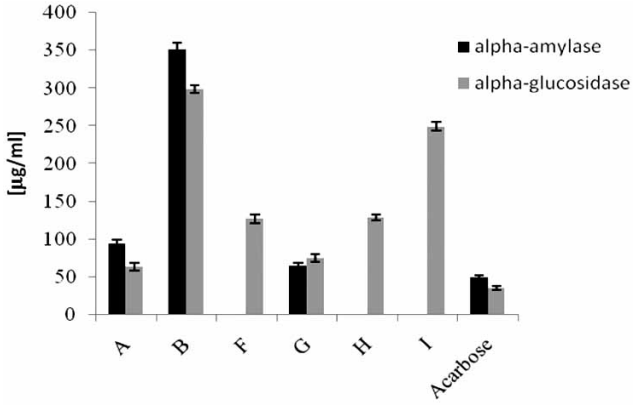


Fig. (2). α-Amylase and α-glucosidase inhibitory activity of chloroform extracts from Lebanese traditional medicinal plants (IC_{50} μg/ml). *C. origanifolia* (**A**), *S. thymbra* (**B**), *P. asperula* (**C**), *S. perfoliata* (**D**), *A. glomerata* (**E**), *H. officinalis* (**F**), *E. centaurium* (**G**), *M. radiatum* (**H**), *S. acetabulosa* (**I**). IC_{50} values are mean ± S.D. (n = 3).

A recent study [61] provided *in vitro* evidences for the potential inhibition of α-glucosidase and α-amylase enzymes, followed by a confirmatory *in vivo* study on rats, of the ethanolic extract of *Andrographis paniculata* and its major constituent andrographolide. The extract showed appreciable α-glucosidase inhibitory effect in a concentration-dependent manner with an IC_{50} value of 17.2 mg/ml and a weak α-amylase inhibitory activity (IC_{50} of 50.9 mg/ml). Andrographolide demonstrated a similar α-glucosidase and α-amylase inhibitory activity (IC_{50} values of 11.0 mg/ml and 11.3 mg/ml, respectively). The *in vivo* studies demonstrated that *A. paniculata* extract significantly reduced peak blood glucose and area under curve in diabetic rats when challenged with oral administration of starch and sucrose. Further, andrographolide also caused a significant reduction in the glucose peak in blood and in the area under the curve in diabetic rats.

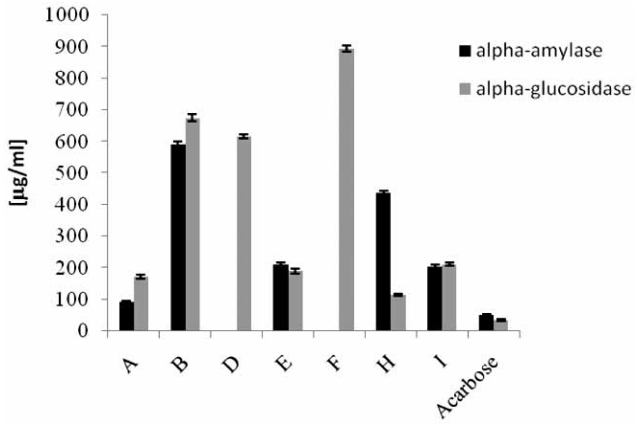


Fig. (3). α-Amylase and α-glucosidase inhibitory activity of hexane extracts from Lebanese traditional medicinal plants (IC_{50} μg/ml). *C. origanifolia* (**A**), *S. thymbra* (**B**), *P. asperula* (**C**), *S. perfoliata* (**D**), *A. glomerata* (**E**), *H. officinalis* (**F**), *E. centaurium* (**G**), *M. radiatum* (**H**), *S. acetabulosa* (**I**). IC_{50} values are mean ± S.D. (n = 3).

Different Brazilian and Mexican plants were studied for their hypoglycaemic activity. Among them, acetone extracts of *Spatoglossum schroederi* and *Caulerpa racemosa* showed an inhibitory activity with IC_{50} values of 0.58 and 0.09 mg/ml, respectively [62]. The butanolic extracts of three Mexican plants, such as *Cecropia obtusifolia*, *Acosmium panamense*, and *Malmea depressa*, with respect to their α-glucosidase inhibition activity, were studied [63]. *C. obtusifolia* (IC_{50} value of 14 μg/ml) exerted the most powerful inhibitory activity, closely followed by *M. depressa* (IC_{50} value of 21 μg/ml), with *A. panamense* being less effective (IC_{50} value of 109 μg/ml). The nature of some of the compounds found in these extracts (phenolics, flavonoids and their glycosides) are in accordance with those mentioned by Jung *et al.* [64] as being effective inhibitors of α-glucosidases.

The prevention and treatment of non-communicable diseases by using the beneficial biological effects of polyphenolic plants have attracted increasing interest from nutritional scientists. The α-glucosidase inhibitory activity of aqueous and methanolic extracts from twenty-eight common Vietnamese edible plants, comprising four groups (plants used for making drinks, edible wild vegetables, herbs, and dark green vegetables), were investigated [65]. The extracts from

plants used for making drinks showed the highest α-glucosidase inhibition, followed by edible wild vegetables, herbs, and dark green vegetables. In particular, *Syzygium zeylanicum*, *Cleistocalyx operculatus*, *Horsfieldia amygdalina*, and *Careya arborea* demonstrated high α-glucosidase inhibitory activity (93, 76, 68 and 67%, respectively) at the concentration of 0.8 mg lyophilized material/ml solution.

Seven exotic/indigenous medicinal plants from Mauritius, namely *Coix lacryma-jobi, Aegle marmelos, Artocarpus heterophyllus, Vangueria madagascariensis, Azadirachta indica, Eriobotrya japonica* and *Syzigium cumini*, were evaluated for their ability to inhibit α-amylase [66]. The results showed that only A. heterophyllus significantly inhibited α-amylase activity. To confirm the observed effects, a further biochemical assay was undertaken to investigate the effects of A. heterophyllus on enzyme inhibition using rat plasma in vitro. It was found that the aqueous leaf extract significantly inhibited α-amylase activity in rat plasma. However, in both cases dose dependency was not observed. Enzyme kinetic studies using the Michaelis-Menten and Lineweaver-Burk equations were performed to establish the type of inhibition involved. In the presence of the plant extract the maximal velocity (Vmax) remained constant (1/150 g/l/s) whereas the Michaelis-Menten constant (K_m) increased by 5.79 g/l, indicating that the aqueous leaf extract of A. heterophyllus behaved as a competitive inhibitor. This study confirm that A. heterophyllus could act as a 'starch blocker' thereby reducing post-prandial glucose peaks.

Kim *et al.* [67] investigated the inhibitory activity of bark pine and needle extracts against both saliva and pancreas α-amylase and α-glucosidase from *Saccharomyces cerevisiae* and porcine small intestine. Both extracts showed similar inhibitory activities against α-amylase. According to origin, inhibitory activity against α-amylase from saliva was more effective than that from the pancreas. Inhibition mode of pine bark extract was investigated. The pine bark extract had an α-amylase inhibitory activity similar to that of acarbose against human salivary and porcine pancreatic glands. However, it was found a combination of non-competitive inhibition and uncompetitive inhibition from the study of α-glucosidase inhibition of pine bark extract against yeast *S. cerevisiae* α-glucosidase. To determine an extract's industrial usage and stability in digestive organs, the stability of extracts at high temperature and low pH by measuring inhibitory activity on salivary α-amylase, pancreatin α-amylase, and yeast *S. cerevisiae* α-glucosidase by pine bark extract were investigated. From these results, pine bark extract showed that inhibition activity remained more than 90% against salivary, pancreatin α-amylase, and yeast *S. cerevisiae* α-glucosidase.

Polyphenol-rich extracts from soft fruits were tested for their ability to inhibit carbohydrate-hydrolyzing enzymes [68]. All extracts tested caused some inhibition of α-amylase, but there was a 10-fold difference between the least and most effective extracts. Strawberry and raspberry extracts were more effective α-amylase inhibitors than blueberry, blackcurrant, or red cabbage. Conversely, α-glucosidase was more readily inhibited by blueberry and blackcurrant extracts. The extent of inhibition of α-glucosidase was related to their anthocyanin content. For example, blueberry and blackcurrant extracts, which have the highest anthocyanin content, were the most effective inhibitors of α-glucosidase. The extracts most effective in inhibiting α-amylase (strawberry and raspberry) contain appreciable amounts of soluble tannins. Other tannin-rich extracts (red grape, red wine, and green tea) were also effective inhibitors of α-amylase. Indeed, removing tannins from strawberry extracts with gelatin also removed inhibition. Fractionation of raspberry extracts produced an unbound fraction enriched in anthocyanins and a bound fraction enriched in tannin-like polyphenols. The unbound anthocyanin-enriched fraction was more effective against α-glucosidase than the original extract, whereas the α-amylase inhibitors were concentrated in the bound fraction. The LH-20 bound sample was separated, and fractions were assayed for inhibition of α-amylase. The inhibitory components were identified as ellagitannins. This study suggests that different polyphenolic components of fruits may influence different steps in starch digestion in a synergistic manner.

Both the Fenugreek and Balanites (two plants commonly used in Egyptian folk medicine as hypoglycemic agents) extracts were able to *in vitro* inhibit α-amylase activity in concentration-dependent manner. Fenugreek was more potent inhibitor than Balanites. This inhibition was reversed by increasing substrate concentration in a pattern which complies well with the effect of competitive inhibitors. Furthermore, this *in vitro* inhibition was confirmed by *in vivo* suppression of starch digestion and absorption induced by both extracts in normal rats. These findings suggest that the hypoglycemic effect of Fenugreek and Balanites is mediated through insulinomimetic effect as well as inhibition of intestinal α-amylase activity [69].

In order to evaluate the ability of α-amylase inhibition of three *Salsola* species, namely *S. soda*, *S. kali* and *S. oppositifolia*, methanolic extracts were prepared and tested *in vitro* [70]. Data are reported in Table **1**. The methanolic extract of all *Salsola* species possessed a significant inhibitory activity against α-amylase with an IC_{50} value ranging from 0.65 to 0.28 mg/ml. The methanolic extract was subjected to a bioassay-guided fractionation process. As the first fractionation step, the methanolic extract was consecutively partitioned with *n*-hexane, dichloromethane, ethyl acetate, and diethyl ether. The activity of each extract was studied using α-amylase inhibition assay using concentrations ranging from 1 mg/ml to 0.016 mg/ml. The *n*-hexane extracts of *S. kali*, *S. oppositifolia*, and *S. soda* showed IC_{50} values ranging from 0.76 mg/ml to 0.32 mg/ml. Comparing the dichloromethane extracts activity of the three *Salsola* species, *S. kali* showed an interesting IC_{50} value of 0.05 mg/ml; this value is quite the same as that of the positive control. Just *S. oppositifolia* and *S. kali* diethyl ether extracts inhibited α-amylase with IC_{50} values of 0.40 and 0.59 mg/ml, respectively. The ethyl acetate fractions obtained from all species exhibited the highest activity. Among them, the *S. kali* ethyl acetate fraction showed an IC_{50} value of 0.02 mg/ml.

Some *Senecio* species were found to be active as α-amylase inhibitors [71,72]. As shown in Table **2**, the methanolic extract of *S. inaequidens* and *S. vulgaris* possessed a good activity with a percentage of inhibition of α-amylase of

Table 1. α-Amylase Inhibitory Activity of *S. oppositifolia*, *S. kali* and *S. soda* Extracts

Extracts	IC_{50} (mg/ml)
S. oppositifolia	
Methanol	0.655 ± 1.5 **
n-Hexane	0.482 ± 1.8 **
Dichloromethane	0.587 ± 1.4 **
Ethyl acetate	0.193 ± 1.2 **
Diethyl ether	0.399 ± 1.2 **
S. kali	
Methanol	0.217 ± 1.8 **
n-Hexane	0.316 ± 1.4 **
Dichloromethane	0.048 ± 0.2 ^
Ethyl acetate	0.022 ± 0.2 **
Diethyl ether	0.591 ± 1.7 **
S. soda	
Methanol	0.623 ± 1.6 **
n-Hexane	0.756 ± 1.2 **
Dichloromethane	0.177 ± 0.2 **
Ethyl acetate	0.028 ± 0.5 **
Diethyl ether	-

Acarbose was used as positive control (IC_{50} 0.025 ± 0.002 mM). Data are given as the mean of at least three independent experiments ± S.D. Differences within and between groups were evaluated by one-way analysis of variance (ANOVA) test completed by a with a multicomparison Dunnett's test. ** $p < 0.01$; ^ $p > 0.05$ compared with the control experiment.

92.9% and 82.5%, respectively, at the concentration of 1 mg/ml. The activity was also displayed by the dichloromethane extracts at the concentration of 100 μg/ml (82.1% and 90.9% of inhibition for *S. inaequidens* and *S. vulgaris*, respectively). A similar result was obtained with *S. leucanthemifolius* methanolic extract, that showed 78% of inhibition at a concentration of 1 mg/ml (Table **3**). A significant activity was found for the dichloromethane extract with an inhibition of 56.7% at 50 μg/ml. Instead, similar results were obtained with the *n*-butanol extract with a percentage of 89.2% at 100 μg/ml.

Recently, different fractions from *Cardamine battagliae*, an apoendemic Calabrian (Southern Italy), were evaluated for their hypoglycaemic activity [73]. In particular, the *n*-hexane fraction showed an interesting α-amylase inhibition with an IC_{50} value of 0.055 mg/ml. This activity may be probably due to stigmasterol, one of the major constituent of the extract and for which it is previously demonstrated significant hypoglycaemic activity [74]. It is interesting also the activity related with dichloromethane fraction with an IC_{50} value of 0.12 mg/ml, while ethyl acetate fraction showed lower activity with an IC_{50} value of 0.72 mg/ml. Another endemic Calabrian species, *Citrus medica* L. cv Diamante, exhibited an interesting activity. The *n*-hexane peel extract inhibted α-amylase with an IC_{50} value of 0.62 mg/ml [75]. The phytochemical composition of the extract revealed the presence of terpenoids, compounds for which the reported lipophilicity may facilitate access to the enzymatic site [76].

The genus *Capsicum*, which originates from tropical and humid zones of Central and Southern America, includes peppers of important economic value. Several *Capsicum* species exist, three of which are widely spread and have a hot or pungent berry: *Capsicum annuum*, *C. frutescens* and *C. chinense*. The Habanero chili pepper is the fruit of *C. chinense*, a very aromatic variety, and is claimed to be the hottest chili pepper in the world. It is of great interest to know the contribution of an individual food product in the daily nutritional needs and how ripening affect dietary, nutrition and therefore biological properties [77,78]. *C. chinense* cv Habanero hypoglycaemic activity was evaluated at two stages of ripening (immature and mature) [79]. The mature Habanero total extract exhibited an IC_{50} value of 130.67 μg/ml against α-amylase (Table **4**). The α-glucosidase enzyme was inhibited more by the immature total extract (IC_{50} 149.56 μg/ml). In order to evaluate the compounds responsible for the activity, the lipophilic fraction was also tested. Immature *C. chinense* Habanero fruits were able to selectively inhibit α-amylase with an IC_{50} value of 9.88 μg/ml. At this stage of maturity hot pepper is characterized by a high content of phytol and different fatty acids. Tolan *et al.* [80] demonstrated that capsaicin exerted a hypoglycaemic effect in dogs by a complex mechanism which involved pancreas and other peripheral organs, such as the liver and the adrenal medulla. Previously, our research group were tested also the *C. annuum* var. *acuminatum* extract against both digestive enzymes [81]. Comparison of data between the two *Capsicum* species revealed that *C. chinense* Habanero at mature stage of ripening showed a good activity against α-amylase. Interestingly, *C. annuum* var. *acuminatum* at mature stage did not exhibit α-amylase inhibitory activity but exhibited an IC_{50} value of 143.7 μg/ml against α-glucosidase. Compari-

Table 2. α-Amylase Inhibitory Activity of *Senecio inaequidens* and *S. vulgaris* Extracts

	% Inhibition of α-Amylase		
Plant	**Methanol (1 mg/ml)**	**Dichloromethane (100 μg/ml)**	**Dichloromethane (50 μg/ml)**
S. inaequidens	92.89 ± 0.0123	82.12 ± 0.0005	64.66 ± 0.0002
S. vulgaris	82.46 ± 0.0041	90.95 ± 0.0001	59.05 ± 0.0001

All the values are the average of three determination ± S.D. Acarbose was used as positive control.

Table 3. α-Amylase Inhibitory Activity of *S. leucanthemifolius* Extracts

Concentrations (mg/ml)	Methanol	Dichloromethane	*n*-Buthanol
1	78.0 ± 0.0003	96.43 ± 0.0001	92.67 ± 0.0001
0.5	-	83.92 ± 0.0007	90.20 ± 0.0008
0.1	-	82.90 ± 0.0002	89.20 ± 0.0003
0.05	-	56.60 ± 0.0005	28.40 ± 0.0002
0.025	-	32.77 ± 0.0002	-

All the values are the average of three determination ± S.D.; -: no activity; Acarbose was used as positive control.

Table 4. Hypoglycaemic Activity of *C. chinense* Habanero Total Extracts and Lipophilic Fractions

C. chinense Habanero		IC_{50} (μg/ml)	
	Maturity stage	α-amylase	α-glucosidase
Total extract	I	228.50 ± 5.7**	149.56 ± 1.3**
	M	130.67 ± 6.2**	264.92 ± 2.2**
Lipophilic fraction	I	9.88 ± 0.4**	> 1000
	M	29.58 ± 0.8**	> 1000
Acarbose		50.0 ± 0.9	35.5 ± 1.2

Data are given as the mean ± S.D (n = 3). Differences within and between groups were evaluated by one-way analysis of variance (ANOVA) test completed with a multicomparison Dunnett's test. **p < 0.01 compared with the positive control. I: immature stage. M: mature stage.

son of data between the two *Capsicum* species revealed that *C. chinense* Habanero showed a significative activity against α-amylase. A weak activity was observed on α-glucosidase inhibition in comparison with *C. annuum* var. *acuminatum*. A similar pattern of hypoglycaemic activity was observed for immature pepper fruits.

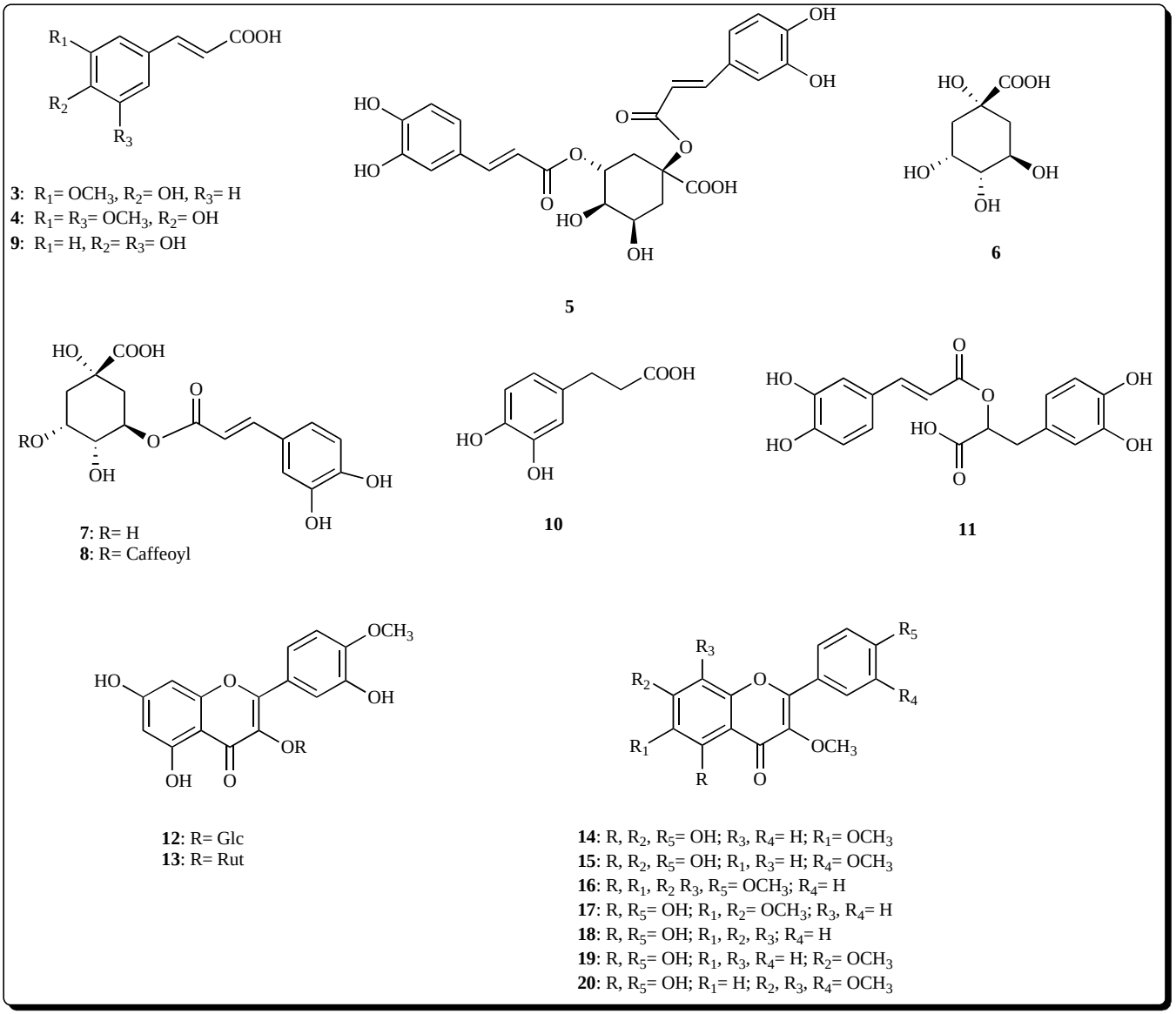
Juniperus oxycedrus is a shrub or small tree growing wild in stony places of the Mediterranean and Near East countries. Juniper berries are used as a spice, particularly in European cuisine, and also give gin its distinguishing flavour. *J. oxycedrus* was used in folk medicine for the treatment of various diseases, among them hyperglycaemia, and obesity [82]. *J. oxycedrus* ssp. *oxycedrus* berry and wood essential oils were investigated for their hypoglycemic activity through the inhibition of α-amylase enzyme [83]. *J. oxycedrus* ssp. *oxycedrus* wood oil exhibited an interesting activity, with an IC_{50} value of 3.49 μl/ml, while the oil obtained from berries exhibited a moderate activity (IC_{50} value > 25 μl/ml). Recently, many studies have reported health benefits against hyperglycaemia and diabetes of some spices, such as *Rhus coriaria* and *Bunium persicum* [84], and grain, such as amaranth (*Amaranthus caudatus*) [85] *via* the inhibition of α-amylase. The methanolic extract of *R. coriaria* and *B. persicum* showed a percentage of inhibition of α-amylase of 36% and 48.3%, respectively, at a concentration of 100 μg/ml. High differences were found in the activity of ethyl acetate extracts which showed 87% of inhibition at 50 μg/ml for *R. coriaria* and 40% at 250 μg/ml for *B. persicum*, respectively. Instead, similar results were obtained for *n*-hexane extracts of both of spices with a percentage of inhibition of 72.3 and 76.6% at 250 μg/ml for *B. persicum* and *R. coriaria*, respectively. TLC analysis revealed the presence of tannins, flavonoids, terpenoids in both methanolic extracts. Flavonoids were present in ethyl acetate extract while terpenoids in *n*-hexane extract of both species. The main compounds so far reported in *Rhus* genus are hydrolyzable gallotannins [86,87] and flavonoids like quercetin, myrcetin and kampferol [88]. It is possible that the inhibition of α-amylase is related to the presence of these compounds which are previously described as α-amylase inhibitors [89,90]. In *B. persicum* the presence of terpenoids is more significative [91] since they are reported to possess hypoglycaemic activity in diabetic and normal mammals, although, the mechanism of action is not clear [92].

Two varieties of *A. caudatus* seeds, Oscar blanco and Victor red, were studied [85]. The methanolic extract showed 50.5% of α-amylase inhibition for *A. caudatus* var. Oscar blanco and 28% for *A. caudatus* var. Victor red at a concentration of 25 μg/ml. High differences were also found in the activity of ethyl acetate extracts which showed 87% of inhibition at 50 μg/ml for var. Oscar blanco and 84% at 250 μg/ml for var. Victor red. Instead, similar results were obtained for *n*-hexane extracts (90% of inhibition at 100 μg/ml) of both varieties.

NATURAL COMPOUNDS AS POTENTIAL HYPOGLYCEMICS

Polyphenols

The inhibitory effects of different polyphenolic compounds on α-amylase activity were investigated *in vitro* [93].



The study showed that molecules having the ability to form quinones or lactones or substances with a 4-oxo-pyrane structure induced an inhibiting effect on α-amylase activity. The reactivity of those substances not able to form that structures because of methoxy groups (ferulic acid, **3**, sinapic acid, **4**), steric obstructions (cynarin, **5**) or short chain length (quinic acid, **6**) was significantly lower. By comparison of IC_{50} values of chlorogenic acid (**7**, 1.4 mM) and isochlorogenic acid (**8**, 0.56 mM), the steric position of the hydroxyl groups is important for the inhibition rate. The hydroxyl groups of the quinic acid (**6**, IC_{50} > 13.0 mM) portion in the isochlorogenic acid (**8**) are arranged in the same plane. This presumably leads to a more pronounced effect. The free hydroxyl groups in the molecule seem to be necessary for a more distinguished inhibitory effect on α-amylase (IC_{50} of 4.8 mM and > 5.0 mM for caffeic acid, **9**, and ferulic acid, **3**, respectively). Substances with a prevailing quinone structure showed the highest inhibition rates in the class of caffeic acid derivatives. The difference between IC_{50} values of caffeic acid (**9**) and dihydrocaffeic acid (**10**) (IC_{50} > 14.0 mM) demonstrated that the double bound in the propionic acid portion seems to be decisive for inhibitory potency. Molecules of more complicated structure and limited free rotation like cynarin (**5**) (IC_{50} > 2.0 mM) were not able to inhibit the enzyme significantly. A glycosidic component is not essential for the inhibiting effect. This fact suggested that the inhibiting mechanism is not based on a competition against the enzyme (as the mechanism of acarbose effect) but a rather specific binding site. The α-amylase inhibition of phenolic compounds is dose-dependent. High concentrations led to inhibition levels up to 90%. Rosmarinic acid (**11**) (IC_{50} of 1.4 mM) is reported to have inhibitory effects on porcine pancreatic amylase *in vitro* [94]. Herbs containing rosmarinic acid (**9**) as main phenolic component have been used in traditional medicine for a long time in order to treat diabetes mellitus [95].

Two flavonoids, isolated from *S. kali* and identified as isorhamnetin-3-*O*-glucoside (**12**) and isorhamnetin-3-*O*-rutinoside (**13**) showed an interesting hypoglycaemic activity

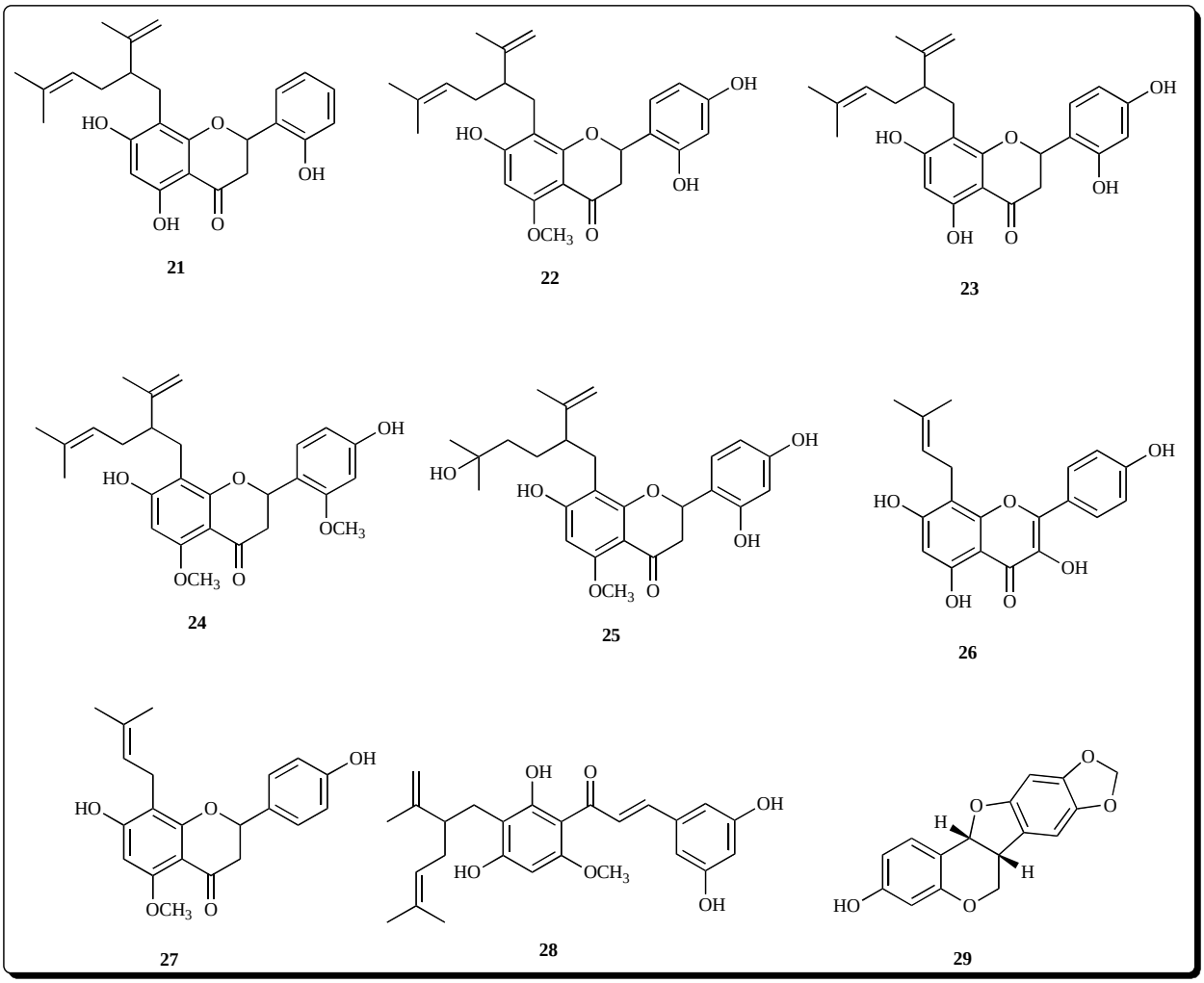
[70]. Compound **12** inhibited α-amylase with an IC_{50} of 0.619 mM, while compound **13** showed an IC_{50} of 0.129 mM. Structure-relationship studies revealed that the rhamnoglycoside moiety plays an important role in the interaction with the enzyme [96].

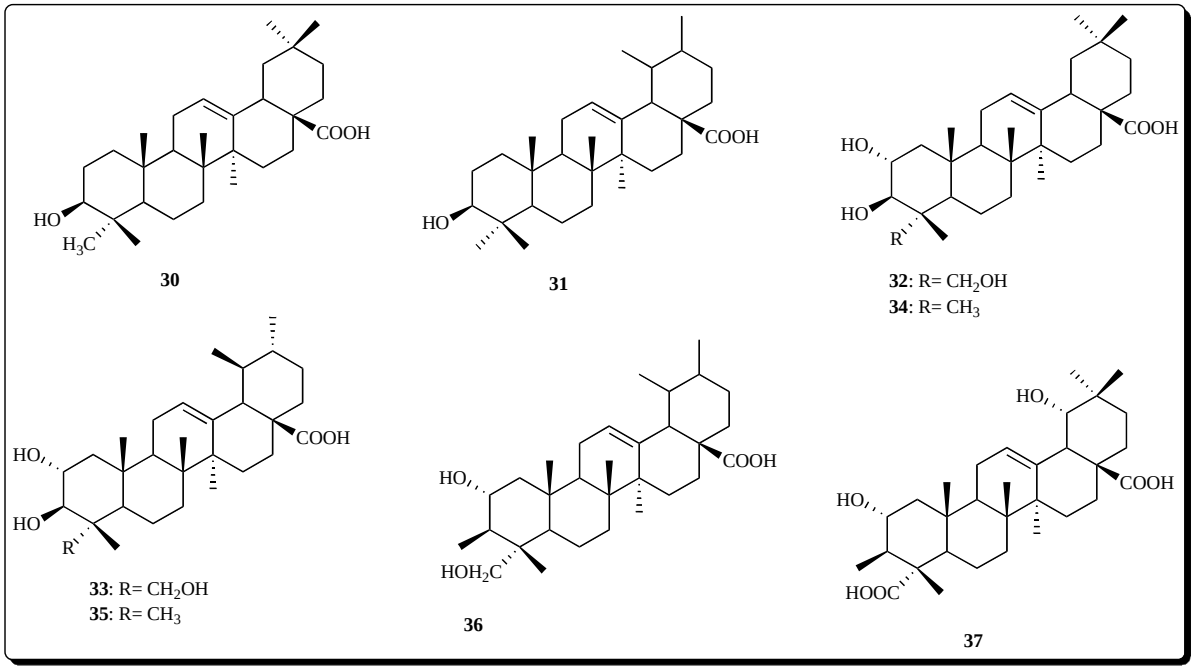
The ethanol and water extracts from *Varthemia iphionoides* aerial parts showed a weak but substantial inhibitory effect on porcine pancreatic α-amylase in the iodine-starch assay, whereas they had a pronounced activity with inhibition of about 70% at a concentration of 200 μg/ml by the 2-chloro-4-nitrophenyl α-maltotrioside (CNP-G_3) degradation method. From the ethanol extract seven 3-methoxyflavones **14-20** were isolated and tested [97]. In the iodine-starch assay, the α-amylase inhibitory activity of the isolated compounds ranged from 18 to 42% at a concentration of 500 μM in decreasing order **18** > **14** > **15** > **16** > **19** > **20** > **17**. In the CNP-G_3 method, the decreasing order of the inhibitory activity was **18** > **14** = **15** = **19** > **17** > **20** > **16**. Compounds **14**, **15**, **18** and **19** almost completely inhibited α-amylase at a concentration of 100 μM. These compounds have more than three hydroxyl groups. The activity of other compounds was in decreasing order **17** > **20** > **16**. The ability of these flavonols to inhibit α-amylase was related to the number of hydroxyl groups in the flavonol structure, which might cause conformational changes in the enzyme structure [98].

The methanol extract of *Sophora flavescens* showed a potent glycosidase inhibitory activity. Active components were identified as kushenol A (**21**), (-)-kurarinone (**22**), sophoraflavanone G (**23**), 2'-methoxykurarinone (**24**), kurarinol (**25**), 8-prenylkaempferol (**26**), isoxanthohumol (**27**), kuraridin (**28**), and maackian (**29**). All flavonoids were effective inhibitors of α-glucosidase [99]. Most flavanones (**21-25**) having 8-lavandulyl group in B-ring potently inhibited α-glucosidase with IC_{50} value of range 30-200 μM. Kushenol A (**21**) which does not bear a 4'-hydroxy group was a good inhibitor (IC_{50} value of 45 μM) of α-glucosidase. Moreover, lavandulylated chalcone, kuraridine (**28**), exhibited an IC_{50} value of 57 μM, which is the first report of a chalcone displaying glycosidase inhibition properties. Thus, 8-lavandulyl group in flavanone skeleton plays a significant role on glycosidase inhibitory activity. Maackiain (**29**) belonging to pterocapan, also exhibited moderate activity against α-glucosidase (IC_{50} 185 μM).

Terpenoids

Triterpenoids such as oleanolic acid (**30**) and ursolic acid (**31**) (2:1 mixture) isolated from *Phyllanthus amarus* are reported to possess a potent α-amylase inhibitory activity with an IC_{50} value of 2.01 μg/ml [77]. Similar triterpene acids were also found in many other antidiabetic plants. Oleanolic





30

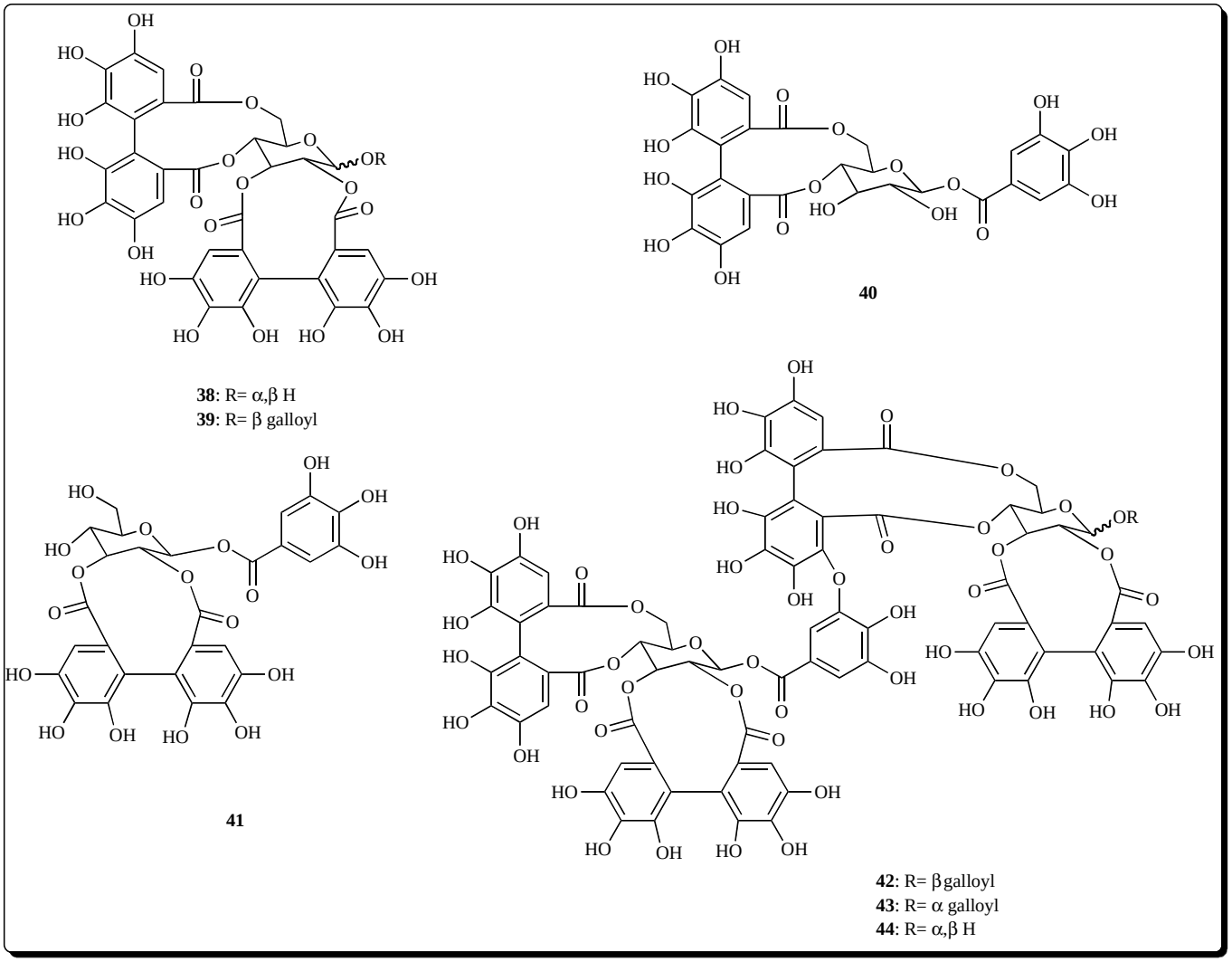
31

32: R= CH_2OH
34: R= CH_3

33: R= CH_2OH
35: R= CH_3

36

37



38: R= α,β H
39: R= β galloyl

40

41

42: R= β galloyl
43: R= α galloyl
44: R= α,β H

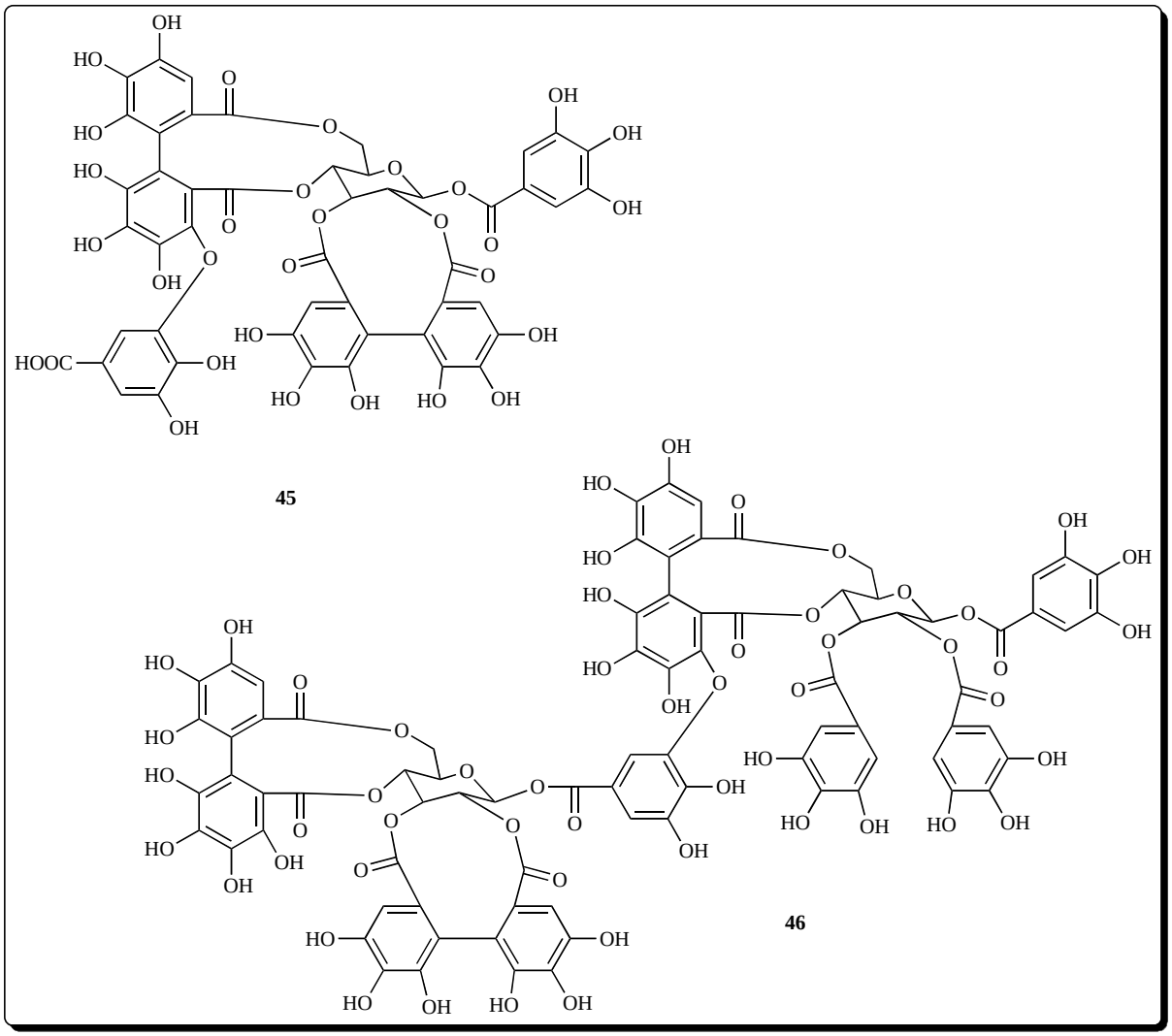
acid (**30**) was isolated from the ethanol extract of olive leaves, *Olea europaea* which are widely recognized as a folk medicine for diabetes and hypertension in Europe [86]. Its glycosides were isolated from the fruit of *Kochia scoporia*, a Chinese and Japanese traditional plant known to prevent and have therapeutic effects in diabetes [100]. Ursolic acid (**31**) and oleanolic acid (**30**) derivatives were also isolated from *Polylepsis australis*, used by the indigenous population of North Western Argentina as infusion for the treatment of diabetes [101].

Six pentacyclic triterpenes, such as oleanolic acid (**30**), arjunolic acid (**32**), asiatic acid (**33**), maslinic acid (**34**), corosolic acid (**35**) and 23-hydroxyursolic acid (**36**), isolated from *Lagerstroemia speciosa*, were recently tested for their effects on α-amylase and α-glucosidase [102]. These compounds showed different inhibitory activities against α-glucosidase while they showed no or weak inhibitory activity against α-amylase. The inhibitory activity of corosolic acid (**35**) (IC_{50} of 3.53 μg/ml) on α-glucosidase was the highest of all inhibitors. Compared to control group, no apparent inhibition against α-amylase was observed except that corosolic acid (**35**) that gave an IC_{50} value of 100.23 μg/ml. Interesting results were obtained also with maslinic acid (**34**) and 23-hydroxyursolic acid (**36**) against α-glucosidase inhibition with IC_{50} values of 5.52 and 8.14 μg/ml, respectively.

Since only corosolic acid (**35**) showed the most significant inhibition, α-glucosidase was treated with **35** using *p*-nitrophenyl (PNP)-glycoside as the substrate to determine the inhibition type. Double-reciprocal plots of enzyme kinetics demonstrated an uncompetitive inhibition of α-glucosidase activity by corosolic acid (**35**). The data revealed that corosolic acid (**35**) was the inhibitor only binded to enzyme-substrate complex in this model. While α-glucosidase was inhibited at various concentrations (2, 3, 4 ug/ml), the K_m value showed an adscendent tendency which was 0.45, 0.29 and 0.23 mM, respectively. According to these data, K_i value of corosolic acid (**35**) which was 3.53 ug/ml could be evaluated. When tested for its hypoglycaemic activity also the triterpene bartogenic acid (**37**), isolated from the methanolic extract of *Barringtonia racemosa*, inhibited intestinal α-glucosidase with an IC_{50} value of 168.09 μg/ml [103].

Tannins

Thirteen tannins, pedunculagin (**38**), 1(β)galloyl pedunculagin (**39**), strictinin (**40**), sanguiin H-5 (**41**), lambertianin (**42**), sanguiin H-6 (**43**), 1-desgalloyl sanguiin H-6 (**44**),



45

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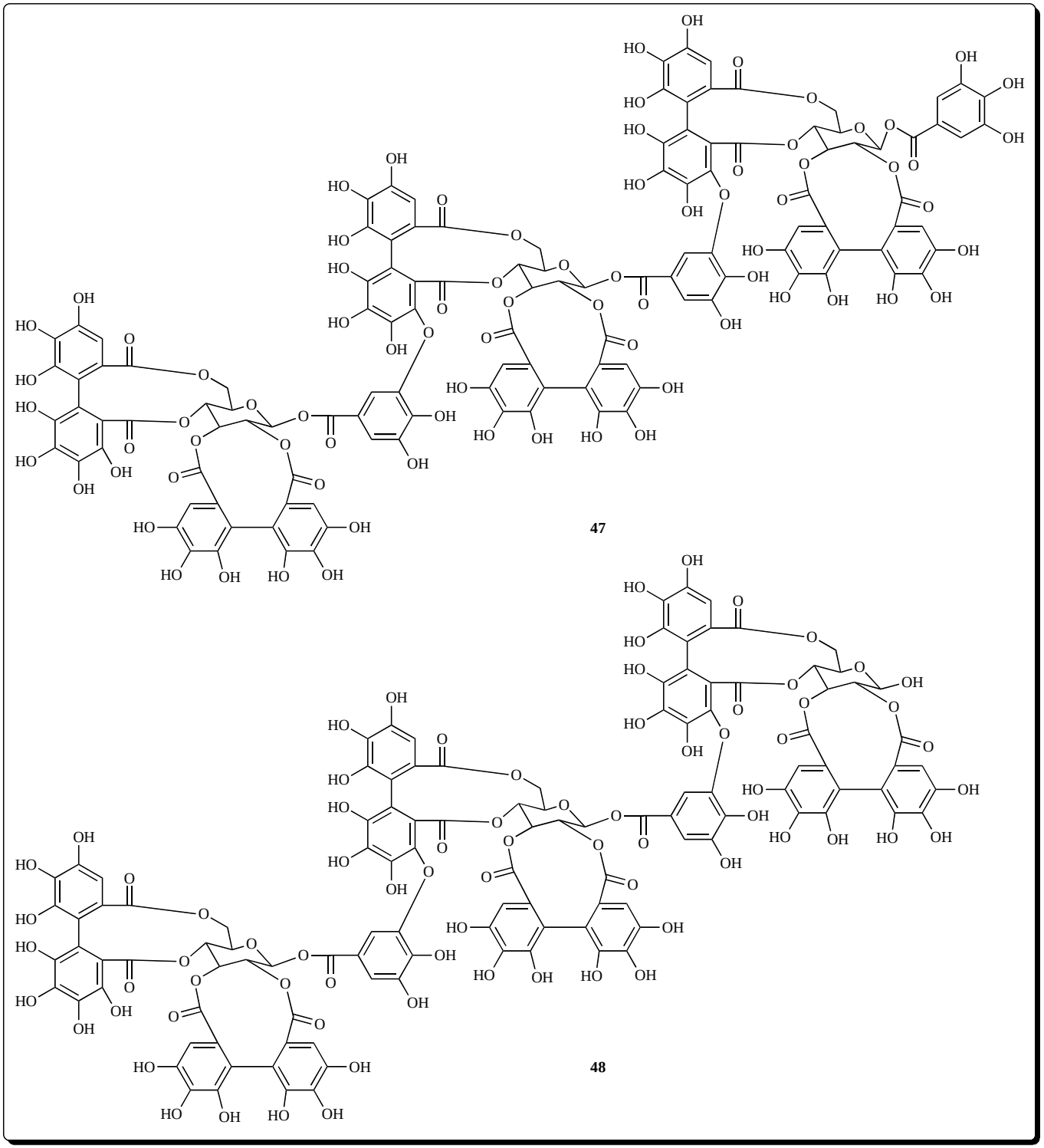
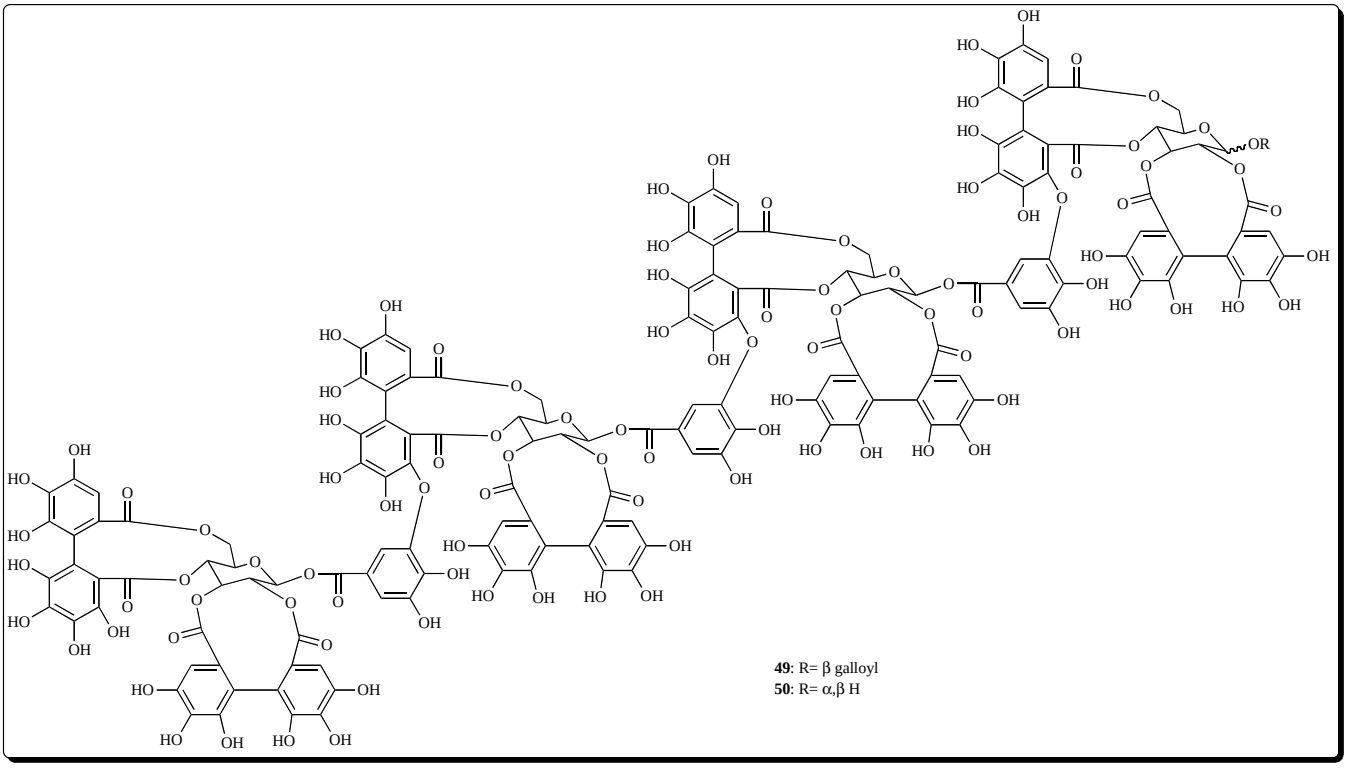


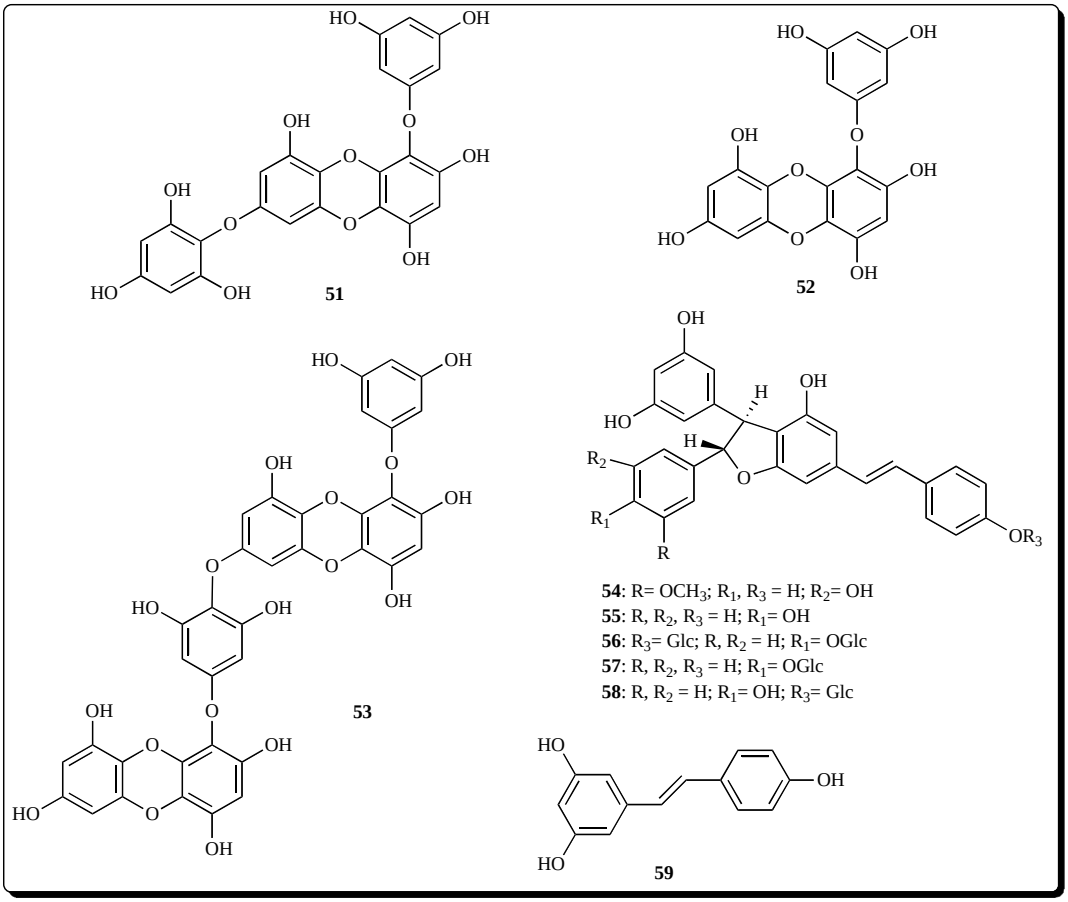
47

48

rubusuaviin A-F (**45**-**50**), isolated from the aqueous acetone extract of Chinese sweet tea (*Rubus suavissimus*) showed an interesting α-amylase inhibitory activity [104]. Rubusuaviin A (**45**) was characterized as 1-*O*-galloyl-2,3-*O*-(*S*)-HHDP-4,6-*O*-(*S*)-sanguisorboyl-β-D-glucopyranose. Rubusuaviins B (**46**), C (**47**), and E (**49**) are dimeric, trimeric, and tetrameric ellagitannins, respectively, in which the sanguisorboyl groups were connected ellagitannin units. Rubusuaviins D (**48**) and F (**50**) were desgalloyl derivatives of rubusuaviins C (**47**) and E (**49**), respectively. The structural differences were reflected in their inhibition of α-amylase. Ellagitannins with β-galloyl groups at the glucose C-1 positions showed stronger inhibition compared with the α-galloyl and desgalloyl compounds. The inhibitory effect was not related to molecular size.



49: R= β galloyl
50: R= α,β H



51

52

53

54: R= OCH_3; R_1, R_3 = H; R_2= OH
55: R, R_2, R_3 = H; R_1= OH
56: R_3= Glc; R, R_2 = H; R_1= OGlc
57: R, R_2, R_3 = H; R_1= OGlc
58: R, R_2 = H; R_1= OH; R_3= Glc

59

Miscellaneous

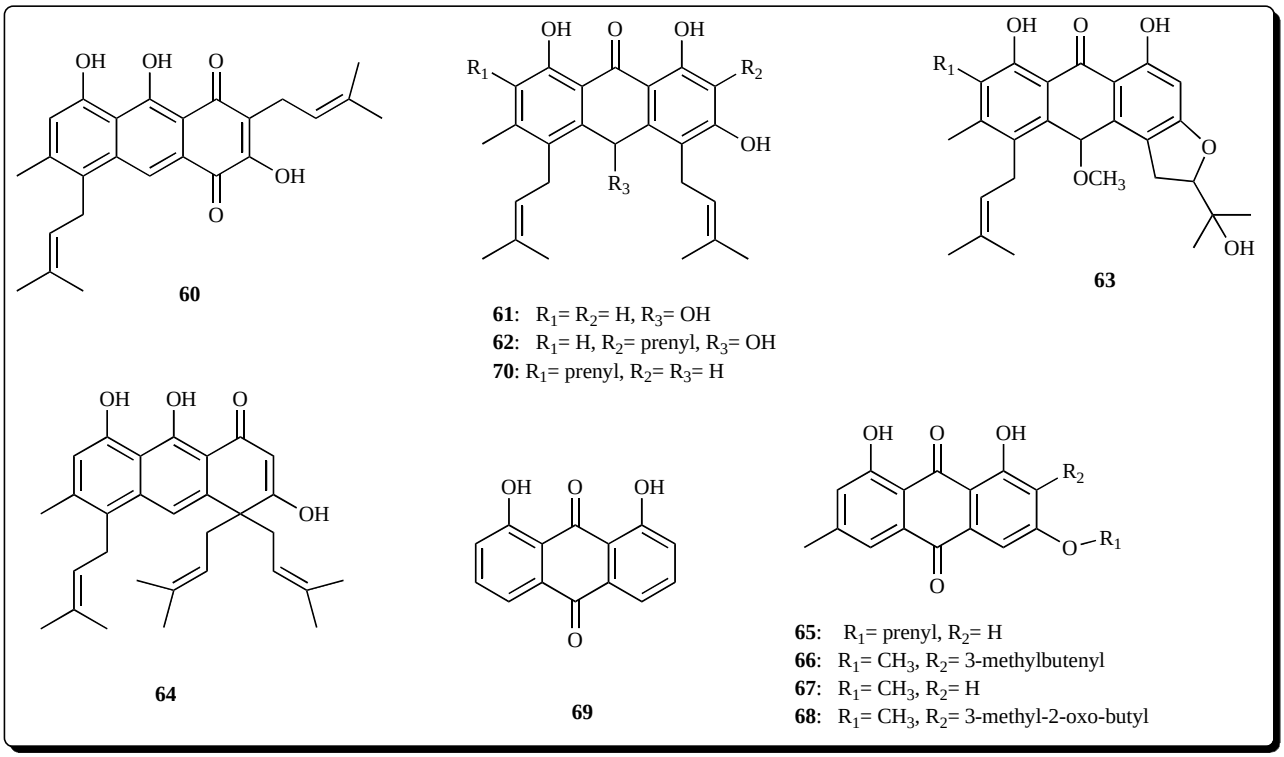
The inhibitory effects of 1-(3',5'-dihydroxyphenoxy)-7-(2",4",6"-trihydroxyphenoxy)-2,4,9-trihydroxydibenzo-1,4-dioxin (**51**), eckol (**52**), and dieckol (**53**), isolated from the brown alga *Eisenia bicyclis*, were tested on α-amylase [105]. The percentage of inhibition was calculated to be 89.5% for **51**, 87.5% for **52**, and 97.5% for **53** at 1 mM. These results suggest that the phloroglucinol derivatives may have an effect on the complications of diabetes.

A 50% EtOH extract of the dried endosperms of *Gnetum gnemon* was purified resulting in the isolation of a new stilbenoid, named gnetin L (**54**), along with five previously identified stilbenoids **55**-**59** (gnetin C, gnemonosides A, C, and D, and resveratrol). Gnetin C (**55**), gnemonoside C (**57**), and gnemonoside D (**58**) inhibited the hydrolysis of starch by α-amylase from porcine pancreas, with IC_{50} values of 203 μg/ml, 840 μg/ml, and 277 μg/ml, respectively [106]. Gnetin L (**54**) and resveratrol (**59**) did not show activity. Considering this result, the hydrophobic benzofuran moiety may lead to lower affinity for the hydrophilic part of the enzyme that recognizes the glucose linkage.

Kengaquinone (**60**), kenganthranols A (**61**), B (**62**), and C (**63**), harunganin (**64**), madagascin (**65**), vismiaquinone (**66**), physcion (**67**), vismiaquinone B (**68**), 1,7-dihydroxyxanthone (**69**), and harunganol B (**70**) were isolated from the *n*-hexane extract of the stem bark of *H. madagascariensis*, that showed strong α-glucosidase inhibitory activity [107]. Compound **62** of the anthranol series showed the highest inhibition at 6.3 μM, which is twice as active as compound **70** (12 μM) and ca. two orders of magnitude higher than established inhibitors such as deoxynojirimycin or acarbose. Perhaps the prenyl group at C-2 is more important for activity than that at C-7. The anthrafurane **63** is less active (21.9 μM) than the anthranols **64** and **70** despite the presence of a prenyl group. Interestingly, the simpler, non-prenylated anthraquinone, the emodine derivative **67**, also showed some inhibitory activity (192.3 μM). However, compounds **66** and **68**, with bulky 3-methylbutenyl and 3-methyl-2-oxo-butyl groups at C-2, were not active. Most of the compounds, but in particular the anthranols **61**-**63** and anthrone **70**, showed significantly higher activities than deoxynojirimycin (425.6 μM), which is one of the most potent α-glucosidase enzyme inhibitors, and acarbose (780 μM), a widely used clinically useful drug. The exceptionally high α-glucosidase enzyme inhibitory activity makes the anthranols **61**-**63** and anthrone **70** interesting leads for drug development.

CONCLUSION

Diabetes is a disorder of carbohydrate, fat and protein metabolism attributed to diminished production of insulin or mounting resistance to its action. Herbal treatments for diabetes have been used in patients with insulin-dependent and non-insulin-dependant diabetes, diabetic retinopathy, diabetic peripheral neuropathy, etc. From the reports on their potential effectiveness against diabetes, it is assumed that the natural compounds have a notable role to play in the management of diabetes, which needs further exploration for necessary development of drugs and nutraceuticals from natural resources. However many herbal remedies used today have not undergone careful scientific assessment and some have the potential to cause serious toxic effects and major drug-to-drug interaction. Continuing research is necessary to elucidate the pharmacological activities of herbal remedies now being used to treat diabetes mellitus.



The object of this review article was to cover the very last advances in research around naturally occurring products as digestive enzymes inhibitors. In fact, one therapeutic approach for treating in the early stage diabetes is to decrease post-prandial hyperglycaemia. This is done by retarding the absorption of glucose through the inhibition of the carbohydrate-hydrolyzing enzymes, α-amylase and α-glucosidase, in the digestive tract. Consequently, inhibitors of these enzymes determine a reduction in the rate of glucose absorption and consequently blunting the post-prandial plasma glucose rise. This work reviewed sixty extracts obtained using different solvents and sixty-six natural products. Majority of published studies have focused on polyphenols inhibitors that are characterized by major activity and selectivity. The knowledge offer from this review should help to provide leads to the ultimate goal of developing new therapeutic drugs more efficacy and safety for the treatment of type 2 diabetes or to prevent the hyperglycemia.

ABBREVIATIONS

BSMA = *Bacillus stearothermophilus* maltogenic amylase

DM = Diabetes mellitus

IC_{50} = 50% Inhibitory Concentration

PNP = *p*-Nitrophenyl

SARs = Structure Activity Relationships

TLC = Thin Layer Chromatography

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