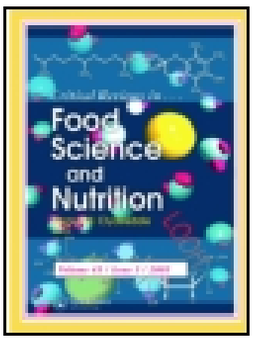

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α-Glucosidase and α-amylase inhibitors from seed oil: a review of liposoluble substance to treat diabetes

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Abstract

One of the effective managements of diabetes mellitus, in particular, non–insulin-dependent diabetes mellitus, is to retard the absorption of glucose by inhibition of carbohydrate hydrolyzing enzymes, such as α-glucosidase and α-amylase, in the digestive organs. Currently, there is renewed interest in plant-based medicines and functional foods modulating physiological effects in the inhibition of α-glucosidase and α-amylase. Accordingly, inhibitors of α-glucosidase or α-amylase derived from various sources have also been isolated, majority of phenolic compounds, and their effects have been investigated in animals as well. As such, when the presence of α-glucosidase inhibitor in many foodstuffs was screened for, we found that vegetable seed oil also strongly inhibited α-glucosidase and α-amylase. Seed oil is an important source of liposoluble constituents with potential for inhibition of these enzymes can also be used as therapeutic or functional food sources. Therefore, this review is aimed at highlighting the main

liposoluble classes of α-glucosidase and α-amylase inhibitors, but it is not intended to be an exhaustive review on the subject.

Keywords

seed oil, fatty acid, α-amylase inhibitor, α-glucosidase inhibitor, anti-hyperglycemic effect

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia, resulting from either impaired insulin action (insulin resistance) or impaired insulin secretion (insulin deficiency). Diabetes meaning "passing through" and mellitus meaning "honey sweet" are in reference to the abundance of sugar detected in blood and urine. It is manifested in two types: type 1 diabetes and type 2 diabetes. Type 1 diabetes constitutes 5-10% of the diabetic population and is characterized by insulin deficiency. Type 1 diabetes has an autoimmune pathology, in which a cell-mediated autoimmune response destroys the insulin-secreting beta cells in the pancreas. It is most commonly diagnosed in childhood. Type I diabetes has not only strong genetic factors, but also has some environmental factors that not to be elucidated. Type 2 diabetes is a metabolic disorder that is characterized by hyperglycemia in the context ofinsulin resistance and relative lack of insulin. Currently there are five major classes of chemically diverse hypoglycemic drugs including: 1) insulin and its analogs, 2) insulinotropic agents, 3) insulin-sensitizing agent, 4) α-glucosidase inhibitors, 5) DPP-Ⅳ inhibitors, with different mechanisms of action. Gliquidone, glipizide, gliclazide, glibenclamide, glimepiride, rosiglitazone, repaglinide, metformin, phenformin, and tolbutamide are widely used for initial treatment of type 2 diabetes mellitus (Figure 1, Li et al. 2010). Use of these synthetic drugs as hypoglycemic agents can lead to gastrointestinal reactions (gastroparesis), skin allergies, and other side effects; the most often observed is hypoglycemia (Pan et al. 2006).

After carbohydrate intake, polysaccharides are first decomposed into oligosaceharides or disaccharides by amylase in saliva or digestive enzymes (amylase) in pancreas. α-Amylase (EC 3.2.1.1) is an enzyme that hydrolyses the α-bonds of large α-linked polysaccharides. Found in many tissues, amylase is most prominent in pancreatic juice and saliva (Hur et al., 2011). In small intestine, oligosaccharides are hydrolyzed to monosaccharides, such as glucose and fructose, by α-glucosidase (EC 3.2.1.20, α-D-glucoside glucohydrolase) secreted from intestine epithelial cells. Only the monosaccharides can enter into the blood circulation system and be utilized by human body. α-Glucosidase catalyzes the final step in the digestive process of carbohydrates. Its inhibitors can retard the uptake dietary carbohydrates and suppress postprandial hyperglycemia and could be useful for treating diabetic and/or obese patients (Nathan et al., 2009). Numerous α-glucosidase inhibitors have been screened from plants, some of which are of clinical importance. Although several drugs targeted for carbohydrate hydrolyzing enzyme are in clinical use, a large inhibitor pool is required as diabetic patients can develop resistance to current regimens. Much effort has been extended in search of effective α-amylase and α-glucosidase inhibitors from the natural resources in order to develop physiologically functional food or to introduce a natural antibiotic agent (Saito et al., 1998; Sels et al., 1999; Stand et al., 1999; Gao et al., 2008). These agents to inhibit α-amylase and α-glucosidase which do not show any side effects (Watanabe et al., 1997; Li et al., 2005; Matsui et al., 2007; Kim et al., 2008).

In the same vein, liposoluble constituents isolated from plant sources, have attracted a great deal of attention in the biomedical arena particularly for their broad spectrum of therapeutic properties and relatively low toxicity (Reddy et al., 2009). The main constituents of plant seed oils are fatty acids, which contribute to human physiology in different ways (Mehmood et al., 2008). With the advancement of biotechnology and pharmaceutical technology, and through many years of research and experiments, the inventors found that unsaturated fatty acids can act as a good α-glucosidase inhibitor. The present invention also discovered that the unsaturated fatty acids in the oily component of mushrooms, plants or animals are effective in controlling blood sugar, and can also be used as functional nutrients for preventing diabetes mellitus.

SERUM GLUCOSE-LOWERING EFFECT OF PLANT-SOURCED LIPIDS Bitter melon is known as a tropical vegetable with healthful effects, which has been traditionally used as a bitter stomachic and an antidiabetic agent (Basch et al., 2003; Dans et al., 2007; Grover and Yadav, 2004). Eleostearic acid is the conjugated linolenic acid typically contained in bittermelon seeds (Chang et al., 1996). Hontecillas et al. (2008) demonstrated that eleostearic acid can decrease fasting plasma glucose and insulin concentrations dependent upon peroxisome proliferator-activated receptor activity in diabetic mouse. Besides, kalahari melon seeds oil which can be also used medicinally for treatment of diabetes and as a purgative and emetic (Van Wyk and Gericke, 2000). The content of vitamin E in pumpkin seeds is very high (Murkovic et al., 1996). Pumpkin seeds oil has been reported to possess cholesterol lowering effect (Jones et

al., 2000) and inhibits the growth of HT-29 human colon cancer cells (Awad et al., 1998). Roselle seed is a valuable food resource on account of its protein and calorie content and also substantial amounts of fiber and valuable micronutrients (Omobuwajo et al., 2000). Conforti et al. (2005) demonstrated that two varieties of *Amaranthus caudatus* L. seeds oil showed α-amylase inhibitory activity (above 80% inhibition rate) at 0.25 mg/mL. The oil obtained from *C. cyminum* seeds was determined for the inhibitory activity against α-glucosidase, at 1 and 0.5 mg/mL, the oil showed 85 and 37% inhibition against α-glucosidase with about 1.8 times less inhibitory activity than acarbose against α-glucosidase at 0.5 mg/mL (Lee, 2005). The lipophilic fraction of *C. annuum var. acuminatum* and *C. annuum var. cerasiferum*, contains high level of vitamin E, β-sitosterol, campesterol and certain fatty acids, methyl and ethyl esters. Hypoglycaemic activity was exerted by *C. annuum var. cerasiferum* with an IC_{50} value of 256.8 μg/ml and 356.8 μg/ml against α-amylase and α-glucosidase, respectively (Tundis et al., 2011). These authors also found lipophilic fraction exhibited a remarkable and selective activity against α-amylase in comparison to the total extract. Additionally, our previous study found that oriental melon seed oil is also potent inhibitors of α-glucosidase and α-amylase (Chen and Kang, 2013; Chen et al., 2014).

FATTY ACID

Biological activities

Essential fatty acids (EFAs) are essential for survival and they cannot be synthesized in the body and hence, have to be obtained in our diet and thus, are essential (Das, 2006). There are two

types of naturally occurring EFAs in the body, the ω-6 series derived from linoleic acid (C18:2) and the ω-3 series derived from α-linolenic acid (C18:3). Both ω-6 and ω-3 series are metabolized by the same set of enzymes to their respective long-chain metabolites. 10-hydroxy-8(E)-octadecenoic acid, an intermediate in the bioconversion of oleic acid to 7,10-dihydroxy-8(E)-octadecenoic acid, was found to exhibited a strong inhibition (IC_{50} 0.07 mM) on α-glucosidase (Paul et al., 2010). Kusunoki et al. (2007) administrated ω-3 fatty acid to OLETF rats, an animal model of diabetes, and found that they improved the insulin resistance. ω-3 PUFA-rich diet has been positively linked with optimal infant development, cardiovascular protection (Hu and Willett, 2002), prevention of neurodegenerative diseases (Conquer et al., 2000) and behavioral disorders (Finnegan et al., 2003) as well as improvement of immune defenses (Brunner et al., 2002). Previous study has also confirmed that consumption of ω-3 reduces the risk of diabetes (De Caterina et al., 2007). Protective effects of ω-3 fatty acids in diabetes have been also tested *in vitro* in amodel of chemically induced cytotoxic damage to insulin-producing cells (Das et al., 2001). Ingestion of PUFA-rich diets, particularly enriched in ω-3 fatty acids, has been shown to have antiobesity effects (Mori et al., 1999) and to facilitate insulin action through a number of metabolic effects. Ingestion of both ω-6 and ω-3 fatty acids has been demonstrated to suppress hepatic lipogenesis, reduce the hepatic output of triglycerides, enhance ketogenesis, and induce fatty acid oidation in both the liver and the skeletal muscle (Berge et al., 1999; Julius, 2003; Jump and Clarke, 1999). Insulin sensitivity may improve as a

result of the effects of fatty acid intake on membrane fluidity (Field et al., 1990). Long chain polyunsaturated fatty acids have many overlap actions such as inhibition of IL-6, TNF-α production, and NF-κB activation, increasing the synthesis of endothelial nitric oxide (NO); and both are anti-inflammatory in nature (Dobrucki et al., 2001; Okuda et al., 1997). In addition, a close interaction exists between NO and COX enzymes attesting to the fact that statins, PUFAs, and NO have positive and negative influences among themselves (Sierra et al., 2006). PUFAs are useful in atherosclerosis, coronary heart disease, osteoporosis, stroke, Alzheimer's disease, and inflammatory conditions such as lupus (Okuda et al., 1997).

Studies have shown that oleic acid and linoleic acid enriched low-fat diet improved fasting glucose level in type 2 diabetes (Garg, 1998), and monounsaturated fat diet therapies improved glycemic condition (Garg et al., 1988). Oleic acid effectively decreased low density lipopreotein cholesterol level and protected LDL particles from oxidation *in vivo* as well as reducing adipocyte expression which are involved in the reduction of obesity-induced insulin resistance and type 2 diabetes (Su et al., 2013).

Clinic management of diabetes

Diets high in carbohydrate (55% to 60% of energy) and low in saturated fatty acid (SFA) (<10% of energy) and total fat (<30% of energy) have been widely recommended as medical nutrition therapy for patients with non–insulin-dependent diabetes mellitus (American Diabetes Association). In recent years, studies have provided important information about the potential

beneficial effects for some patients of a diet that is higher in total fat (provided by UFA) and low in SFA. These findings have resulted in the development of modified guidelines for the nutritional management of diabetes (Franz et al., 1994; Diabetes Care, 1982). A high-UFA diet can be used instead of a high carbohydrate diet in patients with diabetes who present with a distinct metabolic profile. Patients with hypertriglyceridemia who do not need to lose weight are candidates for a high-UFA diet. This result is important because weight loss and maintenance of an ideal body weight are associated with favorable effects on plasma triglyceride and HDL cholesterol levels (Adult Treatment Panel II), as well as insulin sensitivity.

Enzyme inhibitors

The main constituents of plant seed oils are fatty acids, including saturated fatty acids (SFA), monounsaturated fatty acid (MUFA) and polyunsaturated fatty acid (PUFA), which contribute to human physiology in different ways (Mehmood et al., 2008). The saturated fatty acids increase the risks of cardiovascular diseases, cancer and autoimmune disorders (Iso et al., 2002), while unsaturated fatty acids show more nutritional value (Aronson et al., 2001). Although the unsaturated fatty acids of the invention are not structurally similar to carbohydrates, their action on the enzyme also belongs to the competitive inhibition. That is, the inhibitor may bind to a specific binding site of the enzyme. This inhibitor did not affect the Vmax but increased the Michaelis constant (Km). The major purpose of the invention is the use of one or more unsaturated fatty acids alone or in combination through oral or intravenous administration to

prevent or to treat diabetes. The unsaturated fatty acids of the invention can also be used as essential nutrients for human body, in addition to act as the α-glucosidase inhibitor. In general, unsaturated fatty acids are essential fatty acids to human body, so they would not produce side effects as traditional oral hypoglycemic agents do. According to the number of double bonds, unsaturated fatty acids can be divided into monounsaturated fatty acids and polyunsaturated fatty acids. Previously studies reported that fatty acids can be used to inhibit various enzymes such as microsomal glucose 6-phosphatase (Pande and Mead, 1968), human platelet phospholipase (Ballou and Cheung, 1985), hyaluronidases and chondroitinases (Suzuki et al., 2000). Recently, Nguyen et al. (2011) observed that unsaturated fatty acids from Sea Cucumber with strong α-glucosidase inhibitory activity. A previous study reported that methyl palmitate, methyl linoleate and methyl linoleneate inhibited 73.4%, 66.5% and 68.5% of the α-glucosidase activity at a concentration of 200 μmol/mL (Figure 2, Miyazawa et al., 2005). According to these authors, the inhibitory effect increases, with the increase of double bond, thus for fatty acid, existence of double bond was an important factor of inhibition on α-glucosidase (Table 1).

Risk for cardiovascular disease

An epidemiological study by Gillman et al. (1997) suggested that the risk of ischemic stroke in men declined across increasing quintiles of MUFA (and SFA but not PUFA) intake. On the basis of existing evidence that compared the relative cholesterolemic effects of MUFA versus PUFA, Grundy et al. (1997) concluded that for practical purposes, it seems to matter little which

unsaturated fatty acid class replaces SFA in the diet.

PHYTOSTEROLS

Phytosterol structures

Phytosterols are structurally related to cholesterol, but differ in their side chain configuration (Figure 3). There is a wide variety of phytosterol structures but the most frequent phytosterols in nature ate campesterol, β-sitosterol, stigmasterol. 5α-hydrogenation of phytosterols form saturated phytosterols, such as campestanol and sitostanol. Dietary sources of phytosterols usually come from corn, bean and plant oil in humans since they contribute greater amount of dietary phytosterols. It is obvious that vegetarian diets contain higher amount of phytosterols as compared to conventional western diet (Guardiola et al., 2004). Side chain oxidation is believed to be due mainly to enzymatic reactions. The interest in this review has been limited to mono- or dihydroxylated phytosterols with only a few structural changes from the parent sterol

Sources of phytosterols

Phytosterols are enriched in high lipid content plant foods such as nuts, legumes including peanuts, and seeds such as sesame seeds. The concentrations of total phytosterols in specific foods are given in Figure 4. Fruits and grains also contain abundant phytosterols (1-50 mg/100 g) although at lower concentrations as compared to nuts, legumes, and seeds (Trautwein et al., 2006). The food production and refining processes can result in a reduction in phytosterol

content of plant products. Refined olive oil has 81% of the phytosterol content compared to virgin pressed olive oil (Awad et al., 2000). Similarly, refined peanut oil has only 67% of the phytosterol content of unrefined peanut oil.

Phytosterols inhibitors

Phytosterols or plant sterols are natural constituents of plants that belong to the group of isoprenoids. Sunflower seeds, olive oil, and hazelnut oil are rich sources of phytosterols (Azadmard-Damirchi, 2010; Phillips et al., 2005; Phillips et al., 2002). Phytosterols can be separated into three classes based on the presence or absence of methyl groups at the C4 position in the A ring: 4-desmethylsterols (without a methyl group), 4-monomethylsterols (one methyl group) and 4, 40-dimethylsterols (triterpene alcohols, two methyl groups) (Azadmard-Damirchi, 2010). An interesting quirk of cucurbit crops is that the seeds and seedlings generally contain high levels of 24b-ethylcholesta-7, 25-dienol and 24b-ethylcholesta-7, 22, 25-trienol, as well as small amounts of phytosterols, which largely disappear as the plants grow to maturity (Fenner et al., 1989). Clinical studies have repeatedly shown that phytosterols taken as dietary supplements, or as supplemental ingredients in foods, reduced serum cholesterol and low-density lipid cholesterol levels in normal and mildly hypercholesteraemic subjects (Hetherington and Steck, 1999). The mechanism involved may relate to inhibition of cholesterol absorption from the intestinal lumen (Jones et al., 1999). In addition to a cholesterol-lowering effect, phytosterols have been suggested to possess anti-inflammatory (Akihisa et al., 2000), antibacterial, antifungal,

antiulcerative, and antitumor activities (Jones et al., 1997; Ling and Jones, 1995). They are also effective in the treatment of benign prostatic hyperplasia, hyperglycemia, and colon cancer (Pegel, 1997). β-Sitosterol, stigmasterol, and campesterol are important phytosterols. As shown in Table 2, β-Sitosterol, β-sitosterol, stigmasterol, and ergosterol are wildly reported to have antidiabetic potential exhibited various mechanisms. Tabussum et al. (2013) reported that β-sitosterol isolated from *Chrozophora plicata* exhibited a strong inhibitory effect on α-glucosidase with an IC_{50} value of 287.12 μM. β-Sitosterol and other phytosterols have been reported to have potent anti-diabetic properties (Alam et al., 2012; Gupta et al., 2011).

VITAMINS

Structures and metabolism of vitamins

Fat-soluble vitamins, including carotenoids and tocopherols, are also present in the seeds. All of the more than 600 known carotenoids are antioxidants, and approximately 50 are vitamins. Vitamins are organic compounds that cannot be synthesized bu human and ther dore must be ingested to prevent metabolic disorders. As shown in Figure 5, Vitamin A including the free alcohol form retinol (Vitamin A1) and the closely related dehydroretinol (Vitamin A2) form, which differs from vitamin A1 by only one double bond. Because the free alcohol form of vitamin A can be toxic to cells, many tissues, most notably the liver, adipose tissue and kidneys, store vitamin A1 and A2 as esters of long chain fatty acids (e.g. retinyl palmitate and retinyl stearate and their vitamin A2 analogues dehydroretinyl palmitate and dehydroretinyl stearate)

(Palace and Brown, 1994). Retinal is the form of vitamin A required for vision. It can also exist in the A2 form. Several isoforms of retinoic acid are generated by conversion of retinol to retinal by alcohol dehydrogenase enzymes and then to retinoic acids by the activity of aldehyde dehydrogenases (Duester, 1996). The rate limiting step for retinoic acid formation is determined by the activity of retinol dehydrogenase (Chen *et al.,* 1995). Retinoic acids are potent morphogens that provide axial patterning information in developing vertebrates (Means and Gudas, 1995). Vitamin A forms can exist as either the trans or cis-isomers (Fig. 5) and activity potency can be greatly different between the two isoforms, particularly for the retinoic acids.

Fat-soluble vitamins inhibitors

β-carotene has historically received the most attention of the carotenoid because of its provitamin A activity and prevalence in many foods (Fairfield and Fletcher, 2002). Evidence from most previous prospective cohort studies generally supports an inverse association between incidences of plasma concentrations of β-carotene in nondiabetic individuals (Bassuk et al., 2004; Ford et al., 1999; Montonen et al., 2004). As the primary fat-soluble antioxidant that protects lipids from peroxidation, α-tocopherol is able to scavenge mutagenic free radicals and inhibit the oxidation of LDL cholesterol, and these abilities have important implications for the prevention of carcinogenesis (Brigelius-Flohe et al., 2002). α-tocopherol was recently reported to have potential inhibitory effect on α-glucosidase (Javadi et al., 2014). Some, but not all, of the short-term randomized trials in patients with type 2 diabetes also showed the beneficial effects of

oral supplementation of α-tocopherol at high doses on risk factors linked to insulin resistance and diabetes, including oxidative stress, blood pressure, lipid metabolism, endothelial function, and insulin-mediated glucose disposal (Darko et al., 2002; Liu et al., 2006; Paolisso et al., 1995; Regensteiner et al., 2003).

MECHANISM ON INHIBITING α-GLUCOSIDASES

Docking results were sorted by the lowest binding energy of the most populated cluster in the cases of convergence. The best docking conformation was chosen based on the lowest binding energy in the cluster with the greatest number of members. Computational docking analysis was generated using PyMOL (http://www.pymol.org). The Ligplot analyses were introduced to understand the indepth interaction pattern between the docked ligands and the active site residues. Ligplot is an essential tool to understand hydrophobic interactions as well as hydrogen bonding pattern (Wallace et al., 1995). The docking analysis (Fig. 6A) predicted that acarbose, as a competitive inhibitor (Brindis et al., 2010) was surrounded by residues Glu277, His351 and Asp352 (Fig. 6D),which are part of the catalytic residues of isomaltase (Yamamoto et al., 2010), and these residues are believed to play critical roles in the catalyticmechanism as the corresponding residues of Glu276, His348 and Asp349 in α-glucosidase (Park et al., 2008). In the case of acarbose, it can be seen that a hydrophobic patch comprising of Tyr71, Phe177 along with Phe157 surround and hold the terminal ring of acarbose. Thus, Ligplot analyses were especially useful in knowing the hydrophobic interaction pattern.

STRUCTURAL ANALYSIS OF ACARBOSE ON A-AMYLASE

Acarbose, the acarviosine unit is linked to a maltose molecule, is particularly well-known, since it is used against diabetic diseases. This molecule appears to be a potent inhibitor of α-amylases. Crystallographic methods have been extensively used to analyze the proteincarbohydrate inhibitor interactions. The strong inhibition is widely attributed to the binding of the cyclitol unit whose half-chair conformation mimics the substrate distortion expected in the transition state. The adjacent glycosidic bond is *N*-linked, preventing enzymatic hydrolysis. According to chemical and enzymatic studies of the degradation of the acarbose molecule, acid hydrolysis allows breakage of both *O*-glycosidic bonds, while enzymatic hydrolysis by α-amylase only allows cleavage of the linkage between the two glucose units (Qian et al., 2001). The widely recognized two-step mechanism originally proposed by Koshland (1953) for retaining glycoside hydrolases requires the presence of two carboxyl-containing amino acids, one acting as an acid/base catalyst and the other as a nucleophile responsible for the formation of the glycosyl-enzyme intermediate (McCarter and Withers, 1994). In view of previous crystallographic data (Qian et al., 1994) (Fig. 7), we suggested that both Asp197 and Glu233 may be required to produce the â-linked glycosyl-enzyme intermediate. McCarter and Withers confirmed the role of Asp197 as the catalytic nucleophile (McCarter and Withers, 1994). Glu233 and Asp300 are hydrogen-bonded to each other, via an intervening water molecule (W555), as well as to the nitrogen atom of the nonhydrolyzable N-glycosidic bond in the

acarbose-PPA complex. As mentioned in previous study, Glu233 (very close to the chloride ion) is the most appropriate candidate for the role of the catalytic acid/base (McCarter and Withers, 1994). We proposed that liposoluble substance inhibited α-amylases may through binding active cites of Asp197 and Glu233. By virtue of the presence of double bonds, unsaturated fatty acids are particularly susceptible to inhibitory modification, and the extent of this is increased as the degree of unsaturation (ie, number of double bonds) increases.

To the best of our knowledge, this is the first review paper on liposoluble substance to treat diabetes. The potential of liposoluble components for inhibition of α-amylase and α-glucosidase has been highlighted in this work. Liposoluble products have both pharmaceutical and nutraceutical potential, with the use of these products as dietary supplements increasingly important approach to both diabetes treatment and prevention. In conclusion, while a number of liposoluble components have already been explored as hypoglycemic-related enzyme inhibitors, given the vast structural diversity that these products possess, there is an array of unexplored chemical entities waiting to be exploited in future work.

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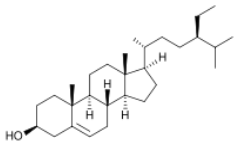
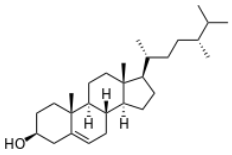
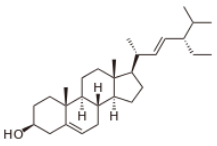
Table 1. IC_{50} values of inhibitory effect on α-glucosidase and α-amylase by fatty acids

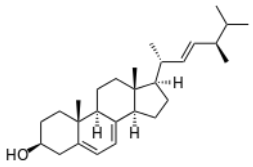
Fatty acid	α-glucosidase inhibition [x)]	α-amylase inhibition [z)]
Methyl linoleate	51.8 μM	NR
Methyl linoleneate	47.5 μM	NR
Methyl linoleneate	46.7 μM	NR
Methyl steareate	24.8 μM	NR
Methyl oleate	20.1 μM	NR
Stearic	22.2 μM	NR
Oleic	64.2 μM	97.3 μg/ml
Palmitic	21.3 μM	38.7 μg/ml
Linoleic	73.8 μM	22.8 μg/ml
Linolenic	17.9 μM	NR

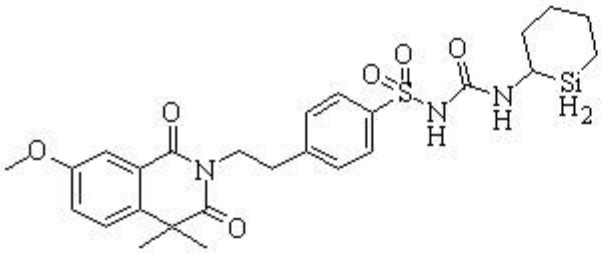
[x)] Modified from Miyazawa et al. (2005) [z)] Modified from previous study (Chen and Kang, 2014);

NR: not reported

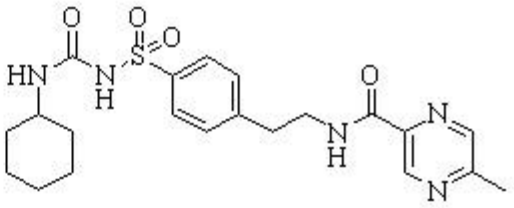
Table 2. Antidiabetic potential of phytosterols

Phytosterols		Anti-diabetic related effect (*In vitro* and in *vivo*)	References
β-Sitosterol		Promising antidiabetic as well as antioxidant effects, rejuvenation of β-cells in β-sitosterol treated STZ-diabetic rats, induced the uptake of insulin from β-cells and produced an anti-hyperglycemic effect through inhibition of α-glucosidase.	Gupta et al., 2011; Ivorra et al., 1990; Ivorra et al., 1998
Campesterol		Anti-diabetic activity and able to ameliorate biochemical damages in alloxan induced diabetic rats	Vetrichelvan and Jegadeesan, 2002
Stigmasterol		Hypoglycemic activity, α-glucosidase inhibitor,	Yoshikawa et al., 1996; Benalla et al.,

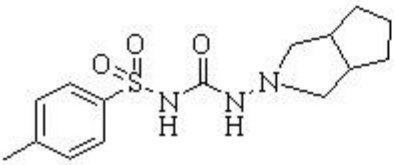
		anti-diabetic and antiperoxidative effect in STZ-induced rat	2010; Subash-Babu et al., 2007
Ergosterol		Shows inhibitory effect against α-glucosidase with IC_{50} of 839.5 μM	Fatmawati et al., 2011



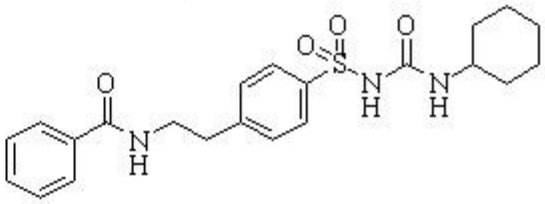
Gliquidone



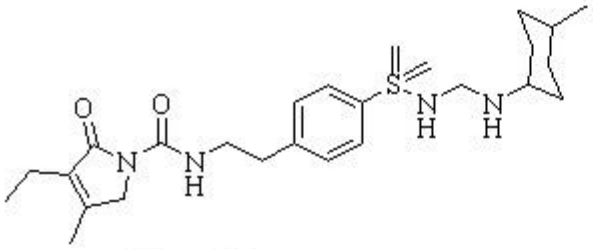
Glipizide



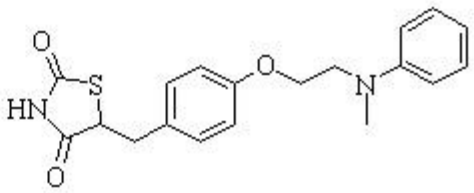
Gliclazide



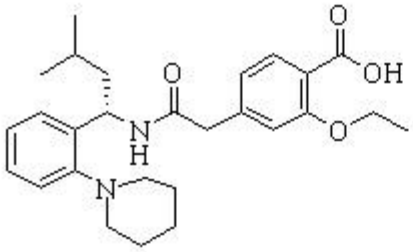
Glibenclamide



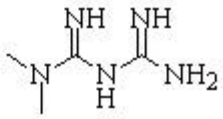
Glimepiride



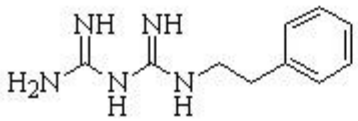
Rosiglitazone



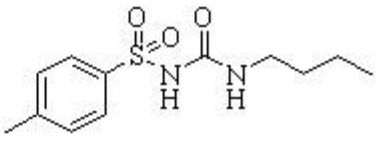
Repaglinide



Metformin



Phenformin



Tolbutamide

Figure 1 Structure of synthetic hypoglycemic agents

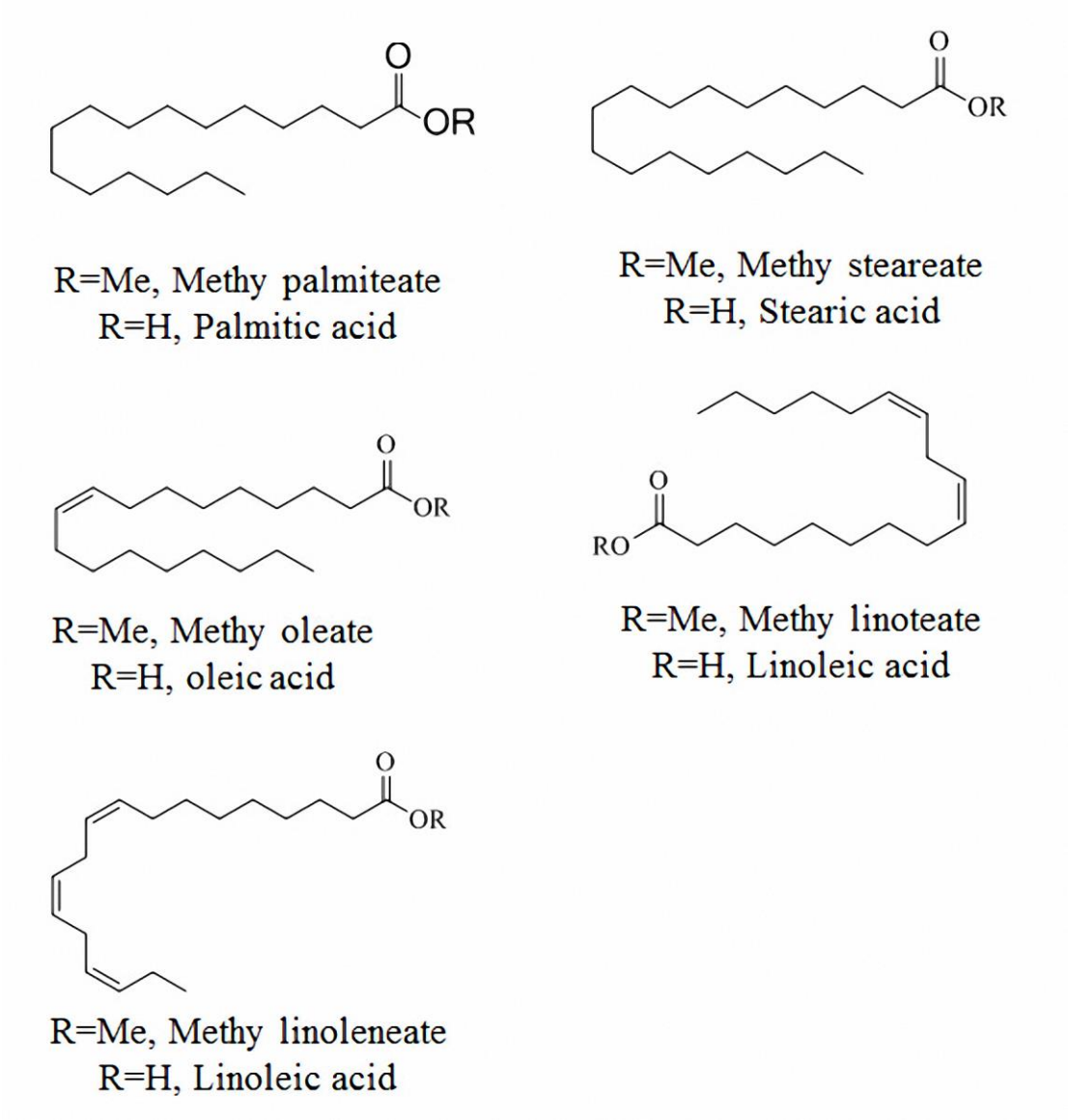


Figure 2 Structure of major fatty acid inhibitors.

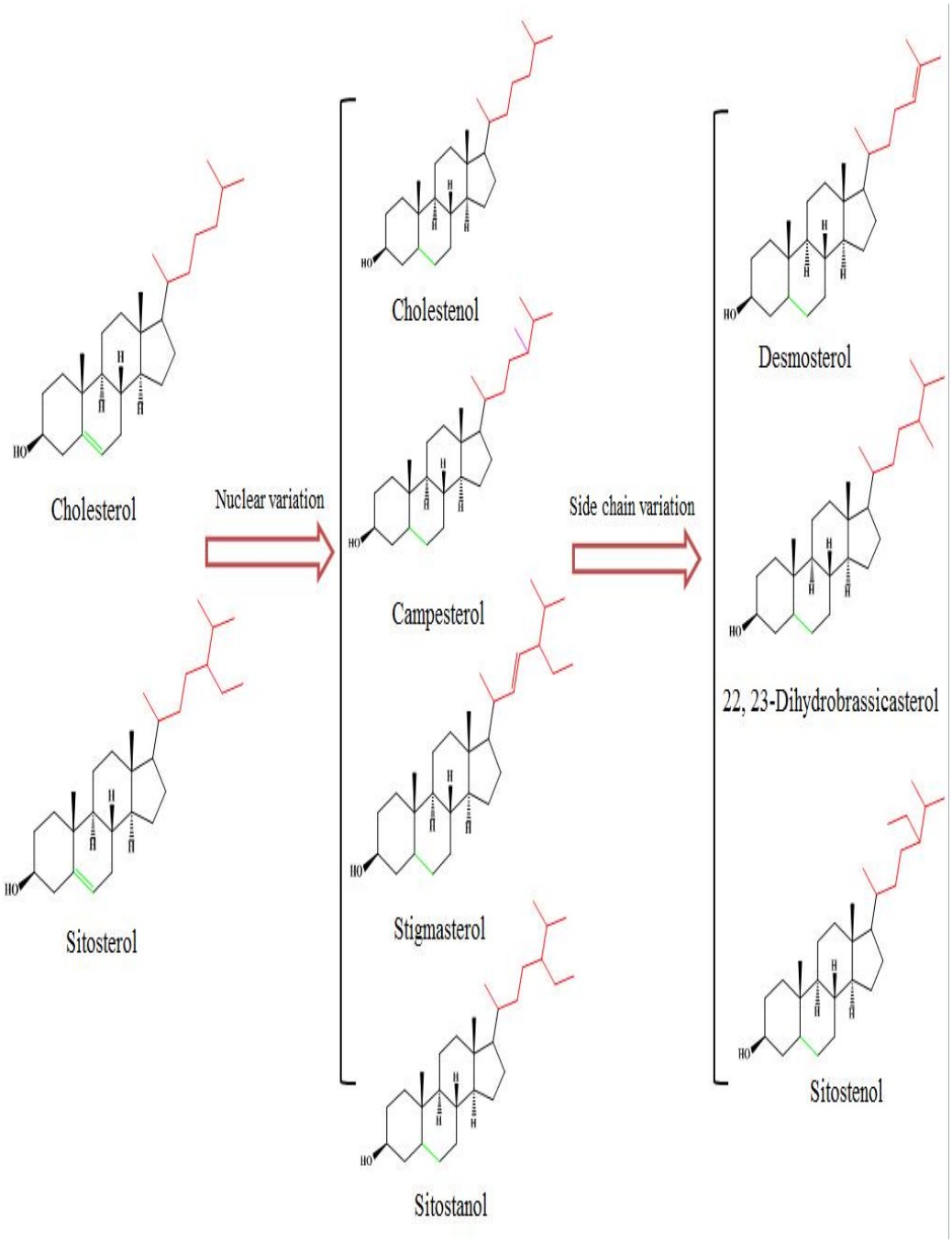


Figure 3 Structure and metabolism of phytosterols

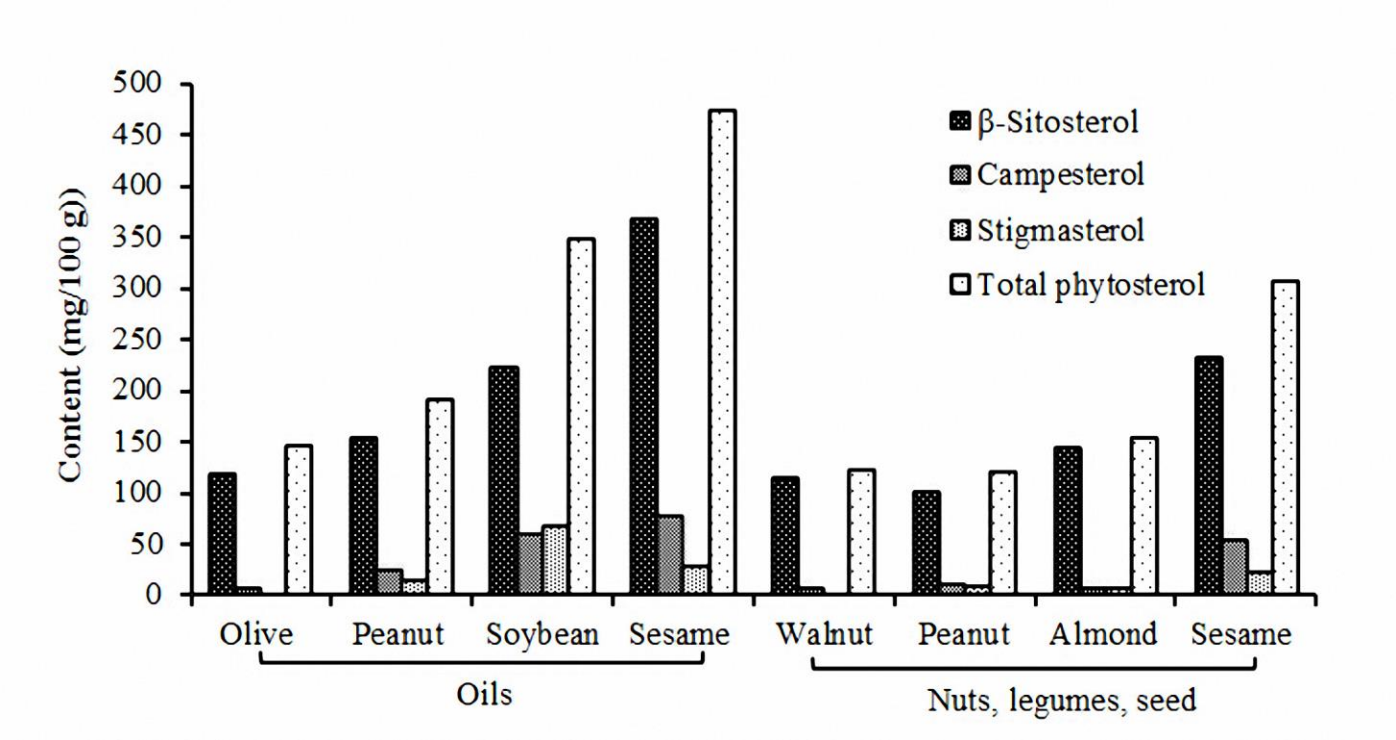


Figure 4 Concentration (mg/100 g) of major phytosterols in high source foods

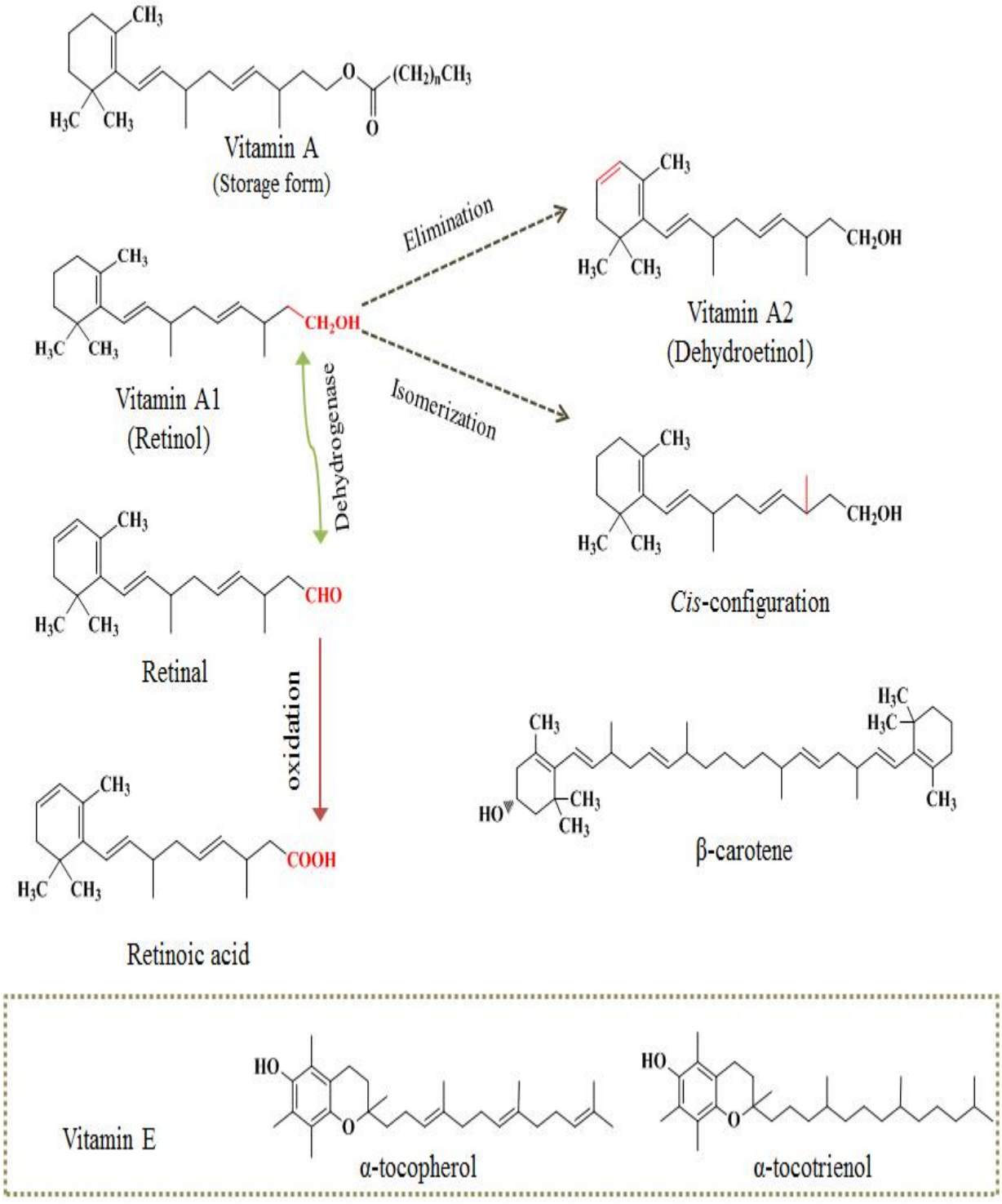


Figure 5 Structure and metabolism of vitamins

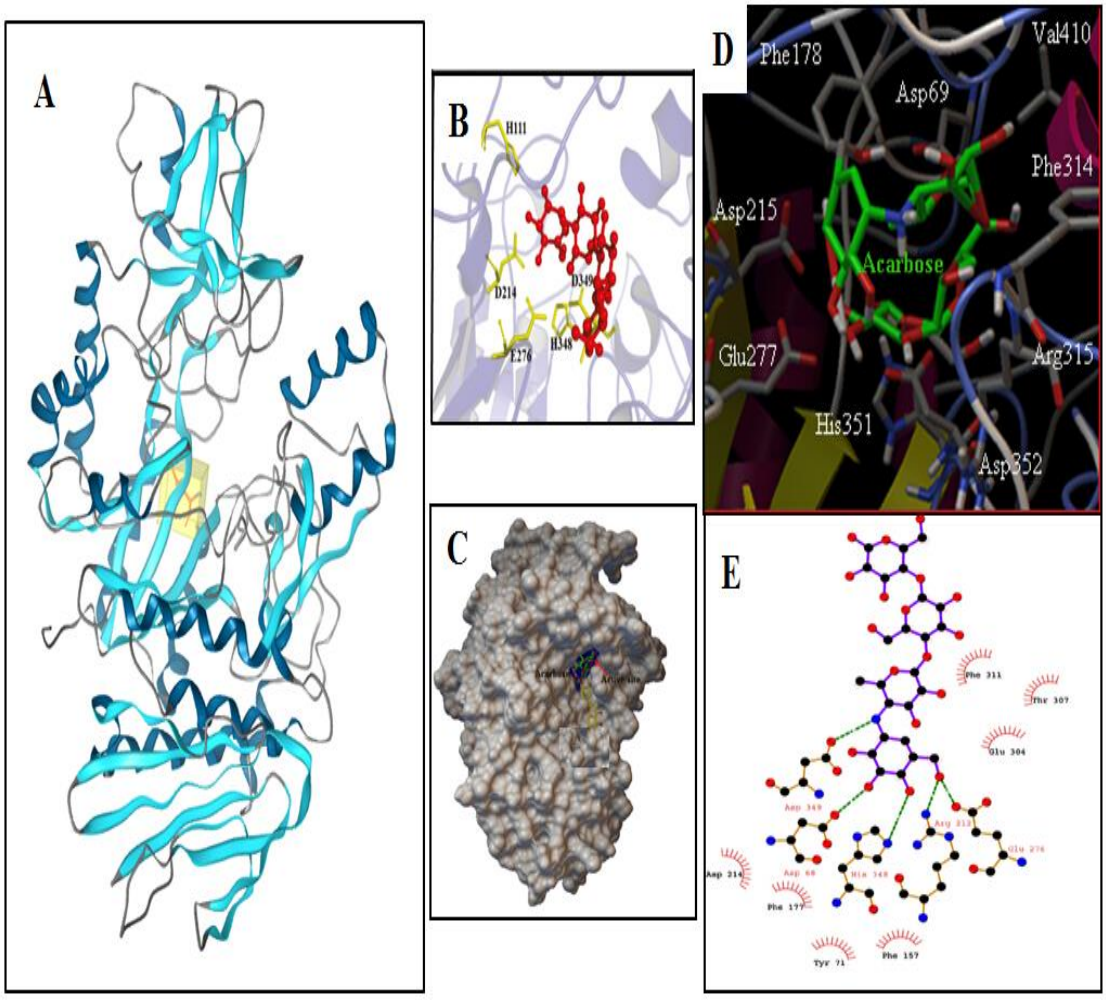


Figure 6 Docking results using the structural model of the α-glucosidase. A: cite of binding of acarbose. B and C: inhibitors inside the binding pocket of α-glucosidase. D: The cartoon represents the α-glucosidase structure with acarbose. E: Acarbose and α-glucosidase interaction analyzed by LIGPLOT adopted from Brindis et al. (2010).

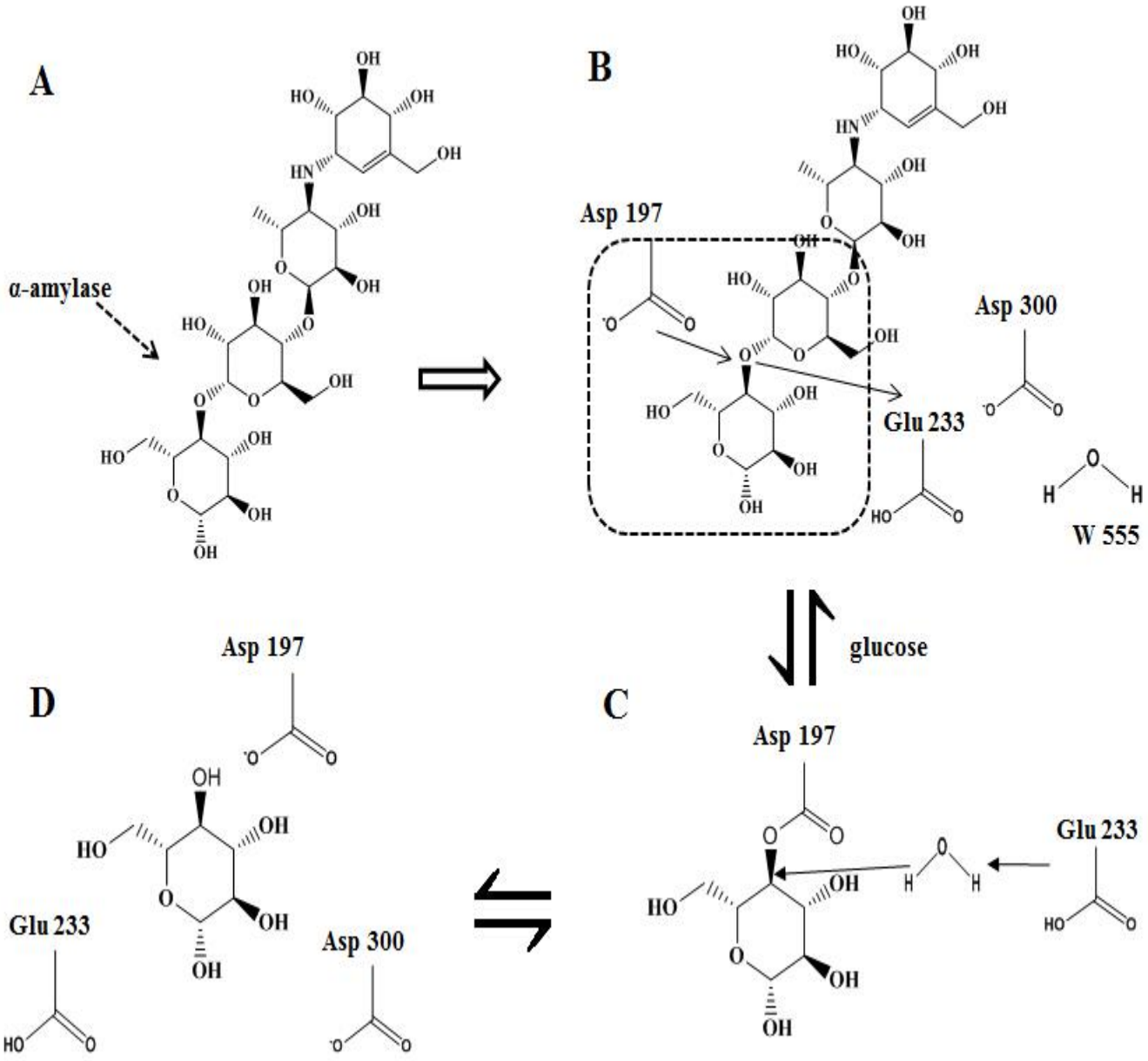


Figure 7 Proposed reaction mechanism for inhibition of α-amylase. A: The arrows indicate the sites of hydrolysis of acarbose by α-amylases. B: The nucleophile, unambiguously identified by McCarter and Withers (1994) as Asp197, attacks the anomeric carbon with concomitant protonation of the glycosidic oxygen by Glu233, widely regarded as a

general acid/base catalyst. C: The resulting covalent α-glycosyl-enzyme intermediate is hydrolyzed by a water molecule activated by the deprotonated Glu233. D The final product with retained anomeric configuration (Qian et al., 2001).