FINAL

Send Orders for Reprints to reprints@benthamscience.ae

Current Medicinal Chemistry, 2016, *23*, 1-37

REVIEW ARTICLE

Updates on Managing Type 2 Diabetes Mellitus with Natural Products: Towards Antidiabetic Drug Development

Fahmida Alam[1,*], Md. Asiful Islam[1], Mohammad Amjad Kamal[2,3,4] and Siew Hua Gan[1,*]

[1]*Human Genome Centre, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia;* [2]*King Fahd Medical Research Center, King Abdulaziz University, Jeddah 21589, Saudi Arabia;* [3]*Enzymoics;* [4]*Novel Global Community Educational Foundation 7 Peterlee Place, Hebersham, NSW 2770, Australia*

ARTICLE HISTORY

Received: May 01, 2016
Revised: June 18, 2016
Accepted: July 08, 2016

DOI: 10.2174/0929867323666160813222436

Fahmida Alam

Abstract: Over the years, natural products have shown success as antidiabetics in *in vitro*, *in vivo* studies and clinical trials. Because natural product-derived drugs are more affordable and effective with fewer side-effects compared to conventional therapies, pharmaceutical research is increasingly leaning towards the discovery of new antidiabetic drugs from natural products targeting pathways or components associated with type 2 diabetes mellitus (T2DM) pathophysiology. However, the drug discovery process is very lengthy and costly with significant challenges. Therefore, various techniques are currently being developed for the preclinical research phase of drug discovery with the aim of drug development with less time and efforts from natural products. In this review, we have provided an update on natural products including fruits, vegetables, spices, nuts, beverages and mushrooms with potential antidiabetic activities from *in vivo*, *in vitro* and clinical studies. Synergistic interactions between natural products and antidiabetic drugs, and potential antidiabetic active compounds from natural products are also documented to pave the way for combination treatment and new drug discovery, respectively. Additionally, a brief idea of the drug discovery process along with the challenges that arise during drug development from natural products and the methods to conquer those challenges are discussed to create a more convenient future drug discovery process.

Keywords: Type 2 diabetes mellitus, natural products, *in vivo*, *in vitro*, antidiabetic drugs, synergistic interaction, drug development.

INTRODUCTION

According to a recent (2013) estimation, approximately 382 million people suffer from diabetes mellitus (DM); this number is projected to be as high as 592 million by the year 2035, which indicates the potential for DM to become the number 1 systemic metabolic disorder worldwide [1]. Type 2 diabetes mellitus (T2DM) is the most prevalent form and ~90 - 95% of DM patients suffer from T2DM. In T2DM, hepatic and peripheral tissues become insulin resistant, and there is inadequate insulin secretion as a result of defective pancreatic β-cells [2].

*Address correspondence to these authors Human Genome Centre, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia;
E-mails: alam.fahmida@yahoo.com; shgan@usm.my

There are several groups of antidiabetic drugs available to treat patients with T2DM including sulfonylureas (*i.e.*, Gliclazide), thiazolidinediones (*i.e.*, Pioglitazone), biguanides (*i.e.*, Metformin), dipeptidyl peptidase-4 inhibitors (*i.e.*, Sitagliptin), glinides (*i.e.*, Repaglinide) and α-glucosidase inhibitors (*i.e.,* Acarbose). Unfortunately, none of these antidiabetic drugs are free from adverse effects including the risk of hypoglycemia, gastrointestinal disturbances, weight gain, diarrhea, renal failure and hypersensitivity [3].

Additionally, the expenditure of T2DM treatment is another heath issue. The T2DM treatment cost in the UK was estimated at 21.8 billion pounds (direct cost 8.8 billion pounds and indirect cost 13.0 billion pounds) in 2010/2011 and is projected to be 35.6 bil-

0929-8673/16 $58.00+.00

lion pounds (direct cost 15.1 billion pounds and indirect cost 20.1 billion pounds) by 2035/2036 [4]. According to an Irish population-based retrospective study (n = 12,941), the total cost of antidiabetic medications was approximately 1.9 million Euro [5]. In the US population, the total projected cost of diabetes in 2012 was 245 billion USD (direct cost 176 billion USD and indirect cost 69 billion USD) [6]. In another recent study (2015) with a Singaporean population (n = 500), the estimated mean annual direct cost of T2DM treatment was 2,035 Singapore dollars, among which 23% accounted for the cost of medications [7]. All of the stated data on cost clearly indicate towards an alarming economic issue for managing future T2DM patients.

Natural products represent the enormous source of novel compounds and chemistry, thus it remains the best source of drugs and drugs leads. In previous years, natural products including fruits, vegetables, spices, mushrooms or natural beverages exhibited promising results of T2DM management via inhibiting α-amylase and α-glucosidase, sodium-dependent glucose transporters, gluconeogenic enzymes, aldose reductase, and advanced glycation end products (AGEs); increasing insulin secretion and activity, glucose uptake, and pancreatic β-cell protection; regulating glucose transporter 4 (GLUT4); reducing oxidative stress; and mimicking insulin action [8, 9]. Because of the adverse effects and cost associated with the current antidiabetic drugs, the acceptance and use of natural products as alternative therapies are dramatically increasing. Additionally, natural products have been reported to be potentially involved in synergistic interactions with antidiabetic drugs, which can be a target for combination therapy [10]. Pharmaceutical studies on natural products are continuing to discover and explore lead structures that may facilitate the development of new antidiabetic drugs as a useful template [11, 12].

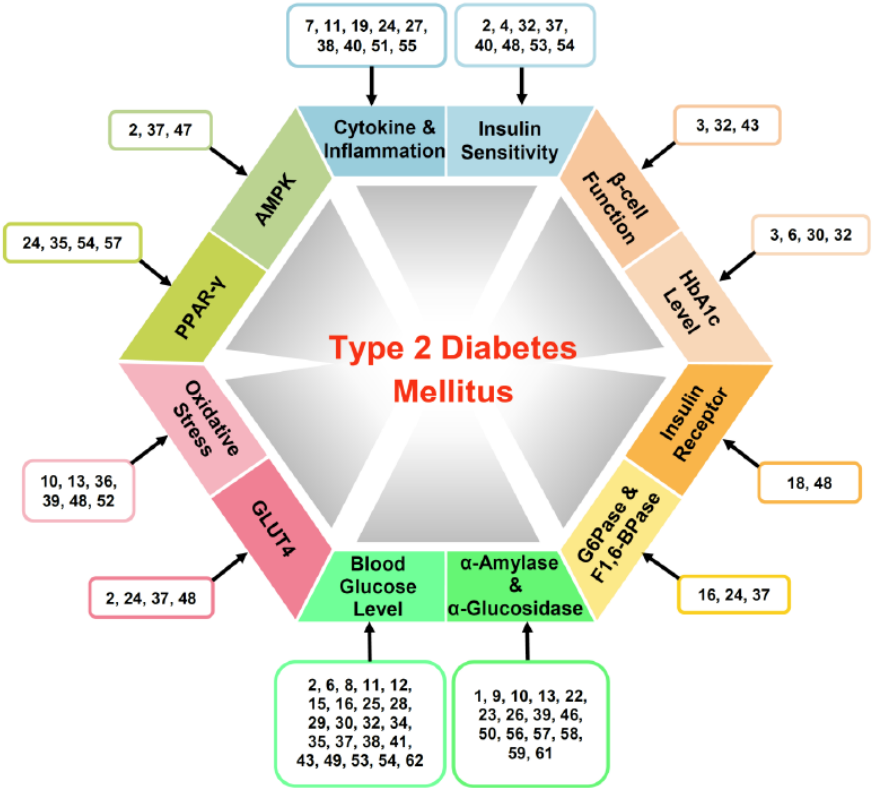
Therefore, the aim of this review was to provide an updated scenario of existing natural products that can potentially attenuate different pathogenic pathways of T2DM development and enhance gene and protein expression involved in T2DM management via *in vitro*, *in vivo* or clinical studies. Synergistic interactions of natural products with antidiabetic drugs are highlighted, and potential active compounds from natural products with antidiabetic activity are documented, which could be considered as a noteworthy source for future antidiabetic combination therapy and drug discovery, respectively. Additionally, the challenges in the way of new drug development from natural products and techniques to overcome those challenges are discussed to make the drug discovery process more feasible in the future.

PATHOPHYSIOLOGY

As an endocrine disorder, T2DM-associated conditions affect the metabolism of all types of food intake including carbohydrates, proteins, fat and water. In hyperglycemic conditions, the elevation of blood sugar levels caused by either inadequate insulin secretion by a defective pancreas or insulin-resistant cells affects the entire metabolic homeostasis. Several factors are associated with the pathogenesis of T2DM (Fig. **1**) and its complications. Sometimes the normal process of metabolism itself becomes pathogenic for T2DM development.

Some enzymes including α-glucosidase (produced in the small intestine) and α-amylase (available in saliva and pancreatic juice) are the major carbohydrate hydrolyzing digestive enzymes. The α-amylase enzyme primarily acts on α-bonds, which finally leads to the production of glucose and maltose by breaking down the long chain of carbohydrates including starch, glycogen and other glucose polymers whereas α-glucosidase enzyme mainly hydrolyzes 1,4-α bonds and breaks down starch and disaccharides into glucose [13, 14]. In T2DM patients, these enzyme activities can worsen the hyperglycemic condition. For this reason, the inhibition of these enzymes is now considered a potential therapeutic approach for the treatment of T2DM, which can significantly decrease the postprandial glucose levels in the blood [15].

A large cluster of glucose transporters (GLUTs), also known as membrane proteins, facilitate glucose transportation inside cells via the plasma membranes. Among the GLUTs which included GLUT 1, 2, 3 and 4, only GLUT4 is responsible for insulin-dependent glucose transport; thus, GLUT4 plays a vital regulator of glucose homeostasis throughout the body and is involved in the pathophysiology of T2DM [16, 17]. In healthy individuals, the translocation of GLUT4 to the cell surface from the intracellular environment occurs in response to insulin binding with the cell surface insulin receptor (IR); further docking and fusion of GLUT4 with the membrane facilitates glucose transport into the cell. In T2DM patients with insulin-resistant conditions, GLUT4 fails to translocate in the cell plasma membrane [18]. Additionally, the defective expression of GLUT4 and inadequate GLUT4 concentrations in T2DM patients further obstructs the reduction of hyperglycemia. Hence, GLUT4 is considered



The numbers included inside the boxes are the code numbers of the natural products listed in Table **2**.

Fig. (1). Potential therapeutic natural products targeting factors associated with T2DM pathophysiology.

one of the potential targets for the metabolic control of T2DM [8].

Glucose-6-phosphatase (G6Pase) and fructose-1,6-bisphosphatase (F1,6-BPase) are the major gluconeogenic enzymes that play vital roles in the gluconeogenesis process in which non-carbohydrate carbon substrates such as pyruvate, lactate or glycerol are converted into glucose [19]. The inhibition of these enzymes can inhibit excess glucose production during the hyperglycemic condition of T2DM patients. Thus, the role of the gluconeogenesis pathway in T2DM pathophysiology can be a good therapeutic target for T2DM management.

The dysfunction and destruction of β-cells is involved in the pathogenesis of T2DM. Normally, pancreatic β-cells play a major role in controlling blood glucose levels by producing, storing and releasing insulin into the blood [20]. During digestion, glucose is produced from carbohydrates and enters the bloodstream. At that time, the rising level of blood glucose is sensed by β-cells, which immediately begin controlling the glucose level by secreting stored insulin and simultaneously producing more. Insulin thereafter stimulates the body cells for glucose uptake from the blood to produce energy [21]. However, in T2DM, several factors such as amyloid deposition, the presence of excessive blood glucose, glucotoxicity, lipotoxicity, incretin hormones, insulin resistance, inflammation, and adipokines lead to the failure or destruction of β-cells [20]. As a consequence, injured or fewer β-cells fail to meet the demand of insulin production during hyperglycemia, finally leading to the development of T2DM. Therefore, the protection of β-cells could be another useful option for T2DM treatment.

Oxidative stress is defined as an imbalance between the production of reactive oxygen species (ROS) and the detoxification of their harmful effects through antioxidants [22]. ROS includes some free radicals such as superoxide ($\bullet O_2^-$), hydroxyl ($\bullet OH$), peroxyl ($\bullet RO_2$), hydroperoxyl ($\bullet HRO_2^-$) and non-radical species such as hydrogen peroxide (H_2O_2) [23]. ROS potentially contributes to T2DM via attacking the healthy body cells and damaging their functional and structural integrity, which consequently leads to many pathophysiological conditions [22]. Oxidative stress also interferes in T2DM pathogenesis through altering the enzymatic systems, lipid peroxidation, impaired metabolism of glutathione and reducing vitamin C levels [24]. There is a close relationship between hyperglycemia

and oxidative stress in T2DM. Hyperglycemia stimulates glucose auto-oxidation as well as the activity of NADPH oxidase, oxidative phosphorylation, protein, glycation and polyol pathway, which finally produce oxidative stress by generating ROS in the body [21] .

CURRENT ANTIDIABETIC DRUGS

Antidiabetic drugs aim to maintain blood glucose levels in the normal range and to reduce diabetes-associated symptoms such as polyuria, ketoacidosis, weight loss, and dehydration. Although insulin is the treatment of choice for T1DM to lower blood glucose levels, several oral antidiabetic drugs with distinct mechanisms exist for treating T2DM [25]. They are designed to either induce insulin secretion by the pancreas, to increase glucose uptake into peripheral tissues by overcoming insulin resistance or to reduce gluconeogenesis by the liver. If the treatment goal is not achieved by these medications, insulin is given in combination.

The major groups of oral antidiabetics are biguanides [26], glinides, sulfonylureas (SU) [27], thiazolidinediones (TZD) [28], α-glucosidase inhibitors [29], dipeptidyl peptidase-4 (DPP-4) inhibitors [30], and glucagon-like peptide-1 (GLP-1) receptor agonists [31]. Metformin and SU are the most widely used for treating T2DM patients [32]. The combination of SU and metformin is also commonly prescribed. Most of the drugs are commonly prescribed in oral dosage form to increase patient compliance [33].

T2DM is a chronic morbid disease that requires treatment throughout life. Hence, the cost of antidiabetic drugs has become a major concern for patient compliance. A study [33] on the calculated cost of drug therapy based on patient bills revealed that the cost of the drugs per prescription was very high; this was assumed to be a cause for patient non-adherence to treatment.

Regardless of the cost, the drugs are associated with several adverse effects that make the patients' lives more miserable. Oral hypoglycemic drugs pose a greater risk of hypoglycemia than when patients are treated with only diet and exercise. However, hypoglycemia is related to various conditions such as mental disorders and stroke [34], hypertension and renal disease [35] and cognitive function [36]. According to a review, SU drugs are significantly associated with severe hypoglycemia in T2DM patients. For example, glimepiride (a type of SU drug) causes approximately 20 - 30% of severe hypoglycemia compared to other SU drugs. Biguanide and TZD drugs were also reported to cause ~45 - 76% and ~15 - 34% of severe hypoglycemia cases, respectively [37]. In addition to hypoglycemia, these drugs are also associated with other adverse effects (Table **1**). Therefore, the quest for developing safer T2DM treatment drugs is still ongoing.

SUCCESSFUL EVIDENCE ON T2DM MANAGEMENT BY NATURAL PRODUCTS

Since 2005, numerous *in vivo, in vitro* and clinical studies have been conducted on natural products to evaluate their potential as antidiabetic agents. Most of the natural products including fruits, vegetables, mushrooms, nuts, natural beverages and oils attenuate the pathogenic factors of T2DM and enhance the expression of beneficial genes and proteins required to control T2DM (Fig. **1**). To provide an updated scenario of T2DM management by natural products, successful *in vivo* and *in vitro* studies (Table **2**), clinical trials (Table **3**) and potential active compounds with antidiabetic activities (Table **4**) are listed. To collect all of the promising evidence of natural products in treating T2DM, a search strategy was developed in which articles in English available in the PubMed database were searched, restricting the year from 2005 (January 1) until 2016 (March 31). Boolean terms (AND & OR) were used and combined the following search strategy-

SEARCH STRATEGY

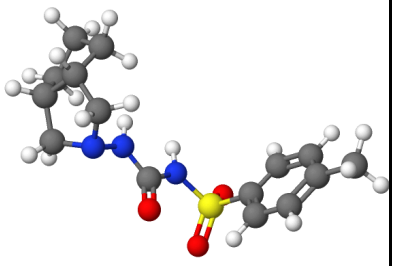
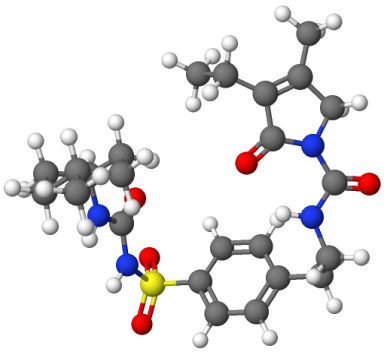
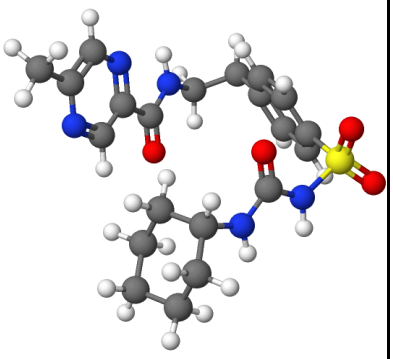
Fruits

[(apple **OR** apricot **OR** applesauce **OR** avocado **OR** banana **OR** blackberries **OR** blueberries **OR** cantaloupe **OR** cherries **OR** dates **OR** dried fruits **OR** figs **OR** fruits **OR** fruit cocktail **OR** grapefruits **OR** grapes **OR** honeydew **OR** melon **OR** kiwi **OR** mango **OR** oranges **OR** papaya **OR** peaches **OR** pears **OR** pineapple **OR** plum **OR** raspberries **OR** strawberries **OR** watermelon) **AND** (type 2 diabetes mellitus **OR** T2DM **OR** non-insulin dependent diabetes mellitus **OR** type 2 diabetes **OR** type 2 diabetic)]

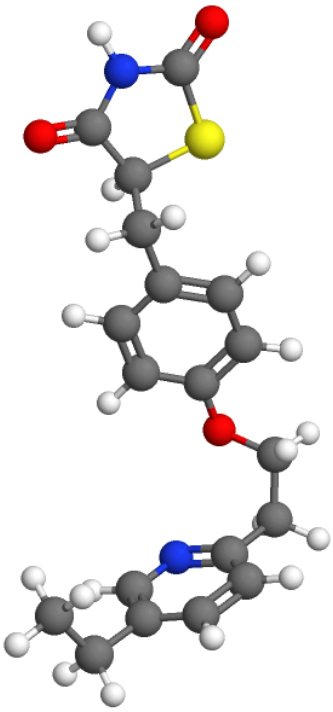
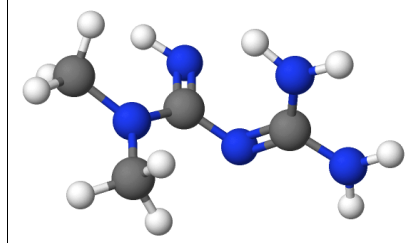
Vegetables

[(amaranth **OR** Chinese spinach **OR** artichoke **OR** artichoke hearts **OR** asparagus **OR** baby corn **OR** bamboo shoots **OR** bean sprouts **OR** beets **OR** Brussels sprouts **OR** Broccoli **OR** green cabbage **OR** Chinese cabbage **OR** bok choy cabbage **OR** Italian beans **OR** green beans **OR** wax beans **OR** bean **OR** cabbage **OR** carrot **OR** cauliflower **OR** celery **OR** cucumber **OR** chayote **OR** daikon **OR** eggplant **OR** garlic **OR** ginger **OR** hearts of palm **OR** jicama **OR** kohlrabi **OR**

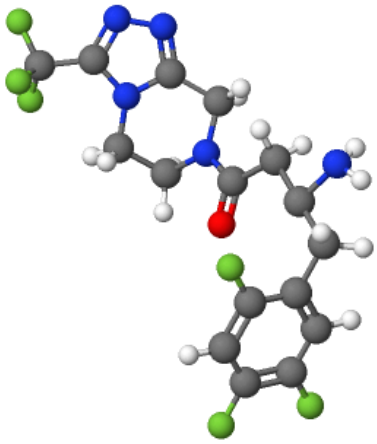
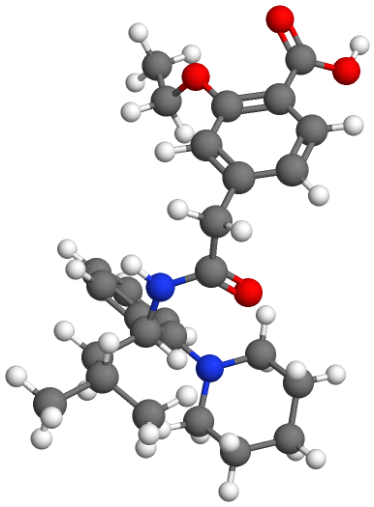
Table 1. Pros and cons of popular oral antidiabetic drugs.

Drugs (Brand names)	Mechanism	Advantages	Side-effects and Limitations	Structure
Sulfonylureas				
Gliclazide (Diamicron, Glimicron, Nordialex)	Selectively binds to sulfonylurea receptors (SUR-1) on the pancreatic β-cell surface, which further stimulates insulin secretion by activating calmodulin	• Anti-atherogenic effect • Protects β-cells from apoptosis induced by hyperglycemia • Reduces insulin resistance in the peripheral area	• Should be taken in conjunction with diet and exercise in which a consistent diet is recommended to reduce the risk of hypoglycemia • Causes disturbances in the gastrointestinal tract • Severe hypoglycemia may be caused by overdose • Interaction with alcohol, β-blockers, phenylbutazone, fluconazole, etc., can potentiate the hypoglycemic action	
Glimepiride (GLIMPID, GLIMY, GLIMPER, GLEAM, Amaryl)	Binds to ATP-sensitive potassium channel receptors on the pancreatic β-cell surface, which consequently depolarizes the membrane and stimulates calcium channels to induce insulin secretion	• Gastrointestinal absorption is complete, with no interference from meals • Does not diminish glucagon secretion in reaction to hypoglycemia compared to glibenclamide • Increases the sensitivity of peripheral tissues to insulin	• Gastrointestinal disturbances, occasional allergic reactions, and rarely blood production disorders including thrombocytopenia, leukopenia, and hemolytic anemia • Risk of hypoglycemia (2 to 4%). • Alcohol consumption and exposure to sunlight can worsen side-effects • Several drugs can potentiate its hypoglycemic action	
Glipizide (Glucotrol, Glibenese, Glibetin, Glipin, Mindiab, Zitrol XR)	Partially blocks the potassium channels' pancreatic β-cells, which depolarizes β-cells and opens the voltage-gated calcium channels, causing insulin release from β-cells	• Gastrointestinal absorption is uniform, rapid and complete	• Drug effect is dependent upon the functioning of β-cells in the pancreas • Overdose can produce hypoglycemia • Alcohol, sugar and sugary food can interact with its action. • Several drugs can increase its hypoglycemic activity	
Thiazolidinediones				

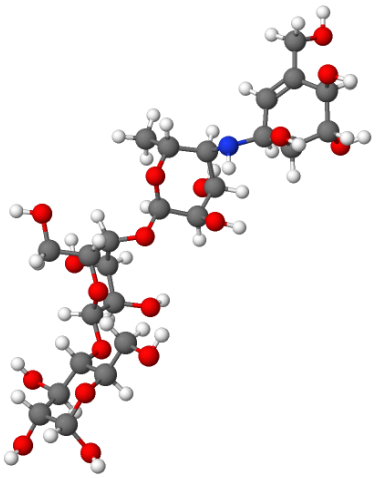
(Table 1) contd….

Drugs (Brand names)	Mechanism	Advantages	Side-effects and Limitations	Structure
Pioglitazone (Actos, Glustin, Glizone, Pioz, Zactos)	Selectively activates the nuclear receptor PPAR-γ to modulate the transcription of the insulin-sensitive genes involved in glucose and lipid metabolism to reduce insulin resistance	• Enhances tissue sensitivity to insulin • Reduces hepatic gluconeogenesis • Improves insulin resistance without increasing β-cell insulin secretion • Decreases triglycerides and increases high-density lipoproteins	• Food slightly delays the absorption rate • Weight gain • Increases the risk of bladder cancer • Safety during pregnancy, lactation (breast-feeding) and in people under 18 is not established yet. • Contraindication exists in patients with heart failure • Causes fluid retention and peripheral edema, may also cause anemia • Upper respiratory tract infection, sinusitis, headache, myalgia and tooth problems are reported • Occasionally causes instances of cholestatic hepatitis • Sulfonylureas or insulin reciprocally exponentiate the risk of hypoglycemia • Acetylsalicylic acid increases the hypoglycemic action • Increases the chance of pregnancy in women taking oral contraception • Gemfibrozil decreases its metabolism • Many drug interactions increase its serum concentration	
Biguanides				
Metformin (Apo-Metformin, Gen-Metformin, Novo-Metformin, Nu-Metformin, Sandoz Metformin)	Activates AMP-activated protein kinase (AMPK) and increases its activity	• Decreases hepatic glucose production • Decreases intestinal absorption of glucose • Improves insulin sensitivity by increasing peripheral glucose uptake and utilization • GLUT4 placement to the plasma membrane, which leads to insulin-independent glucose uptake • Induces weight loss in obese people	• Lactic acidosis occurs rarely • Can interact with alcohol • Consumption without food can lead to gastric irritation • Interaction with several drugs decreases its therapeutic efficacy • Acetylsalicylic acid increases the hypoglycemic action • Can cause dyspepsia, nausea and diarrhea	

(Table 1) contd….

Drugs (Brand names)	Mechanism	Advantages	Side-effects and Limitations	Structure
Dipeptidyl Peptidase IV Inhibitors				
Sitagliptin (Janumet, Janumet XR)	Competitively inhibits the DPP-4 enzyme, which breaks down the incretins GLP-1 and GIP, thus increasing insulin secretion and suppressing glucagon release from the pancreatic α-cells. This drives blood glucose to reach normal levels	• Reduced risk of hypoglycemia • Reduced risk of weight gain	• Rarely causes nausea and common cold-like symptoms • Causes pancreatitis, renal failure, hypersensitivity reactions and severe joint pain • Combination with other drugs (such as metformin) is required for its efficacy • Can be administered without regard to food • Many drug interactions increase its severity of adverse effects	
Glinides				
Repaglinide (GluCoNorm)	Closes ATP-dependent potassium channels in the membrane of β-cells, which depolarizes the β-cells and opens the calcium channels. This induces insulin secretion and lowers blood glucose levels	• Selective for pancreatic β-cells but does not affect other tissues (skeletal or cardiac muscle or thyroid) • Causes slight weight gain, which is lower than that caused by sulfonylureas and insulin • More effectively lowers the postprandial blood glucose than metformin, sulfonylureas and thiazolidinediones	• High-fat meals decrease the AUC and Cmax • Does not possess appreciable hypoglycemic activity • Activity is dependent on the presence of functioning β-cells and glucose (no effect on insulin release in the absence of glucose) • Less effective in reducing fasting blood glucose levels, which requires a longer duration of therapy (~one month) • Safety in pregnant women has not been established • Contraindications exist in people with diabetic ketoacidosis, sinusitis, T1DM, nausea, diarrhea, constipation, vomiting, headache, back pain	
α-Glucosidase Inhibitors				

(Table 1) contd….

Drugs (Brand names)	Mechanism	Advantages	Side-effects and Limitations	Structure
Acarbose (Prandase, Precose, Glucobay)	Reversibly binds and inhibits the pancreatic α-amylase and membrane-bound intestinal α-glucoside hydrolases to further inhibit the hydrolysis of complex carbohydrates into glucose in the small intestine	• Delays glucose absorption • Lower postprandial hyperglycemia	• Should be taken with the first bite of main meals. • Causes hepatitis. • Gastrointestinal side-effects (flatulence and diarrhea) • Many drug interactions increase its hypoglycemic action	

PPAR-γ = Peroxisone proliferator-activated receptor γ, GLUT4 = Glucose transporter 4, DPP-4 = Dipeptidyl peptidase-4, GLP-1 = Glucagon-like peptide-1, GIP = Glucose-dependent insulinotropic polypeptide (gastrointestinal hormones released in response to a meal), AUC = Area under the curve, T1DM = Type 1 diabetes mellitus.

Table 2. Evidence of *in vitro* and *in vivo* antidiabetic activity of natural products reported between 2005 (January) and 2016 (March).

No.	Source	Type of study (model), dose and duration	Activity	Origin	Year, [References]
Fruits and related parts					
1	White grape skin	*In vitro* (enzyme inhibition assay), 50 µL of grape skin extract	• Inhibition of α-amylase and α-glucosidase activity	Italy	2016, [106]
2	Enterolactone (produce from Strawberry lignans)	*In vitro* (rat skeletal muscle-derived cell line, L6 myocytes in culture) *In vivo* (T2DM model db/db mice)	• Increases glucose uptake • Activation of AMPK • Translocation of GLUT4 to the plasma membrane • Suppresses the increased FBG level • Improves insulin resistance and glucose tolerance	Japan	2016, [107]
3	Anthocyanins of fermented berry beverages	*In vitro* (human epithelial Caco-2 cells and iNS-1E pancreatic β-cells)	• Modulates incretin-cleaving DPP-4 and its substrate GLP-1 • Increases glucose stimulated insulin secretion from pancreatic β-cells	USA	2016, [108]
4	Fixed Dose Combination of grape seed extract proanthocyanidin, vitamin C, green tea polyphenols	*In vivo* (KK-ay mice), 2 mg/ 10 g/day and 8 mg/ 10 g/day for 4 weeks	• Attenuates lipid peroxidation • Improves insulin sensitivity • Improves glucose tolerance • Increases the HDL-C content	China	2015, [109]

(Table 2) contd…

No.	Source	Type of study (model), dose and duration	Activity	Origin	Year, [References]
5	Crude polysaccharide of apricot (*Armeniaca sibiricaL. Lam.)* pulp	*In vitro* (enzyme inhibition assay), IC_{50} - 6.06 mg/mL	• α-glucosidase inhibition	China	2015, [110]
6	Combined extracts of grape pomace (skin and stem) (*Vitis vinifera)* and omija fruit (*Schisandra chinensis*)	*In vivo* (male C57BL/KsJ-*db/db* mice), 0.5% grape pomace extract and 0.05% omija fruit extract (*w/w)* for 7 weeks	• Decreases the liver fatty acid synthase and glucose-6-phosphate dehydrogenase • Reduces the hyperglycemia, β-cell failure, HbA1c, plasma insulin, FFA, TG and TC, liver FFA and cholesterol levels	Korea	2015, [111]
7	Grape seed procyanidin B2	*In vivo* (male C57BLKS/J db/db diabetic mice), 30 mg/kg body weight per day for 10 weeks	• Attenuates the elevated body weights, food intake and AGE levels • Increases the islet sizes, insulin levels and HOMA-IR • Attenuates the IL-1β and NLRP3 pro-inflammatory cytokines and MFG-E8 protein level • Provides anti-inflammatory effect	China	2015, [112]
8	Soluble dietary fiber of fermented apricot pulp	*In vivo* (male diabetic Wistar rats), 2 - 200 mg/kg body weight for 28 days	• Decreases blood glucose level and body weight • Inhibition of α-glucosidase activity (IC_{50} - 17.458 mg/mL)	China	2015, [113]
9	Individual methanolic extract of banana *(Musa paradisiaca)*, kiwi *(Actinidia deliciosa)* and apple *(Malus domestica)*	*In vitro* (α-amylase inhibitory assay)	• Inhibition of α-amylase activity	India	2015 [114]
10	Acetone extract of passion fruit (*Passiflora ligularis)* pulp	*In vitro*	• Possess an efficient DPPH•, superoxide and NO radical scavenging activities • Inhibition of α-amylase and α-glucosidase activity	India	2014, [115]
11	Grapefruit (*Citrus x paradisi*) extract	*In vivo* (diabetic male C57BL/6J db/db mice), 0.5 g/kg body weight for 6 weeks	• Decreases the fasting glucose levels • Decreases the mRNA expression of some proinflammatory genes in the liver and visceral fat • Hypermethylation of TNF-α in adipose tissue which may reduce inflammation	Spain	2014, [116]
12	Apple (*Malus domestica* Borkh.) extract	*In vivo* (male C57BL/6N mice), 12.24 mg apple extract	• Reduces postprandial blood glucose levels	Germany	2014, [117]
13	Phenolic extract of avocado pear (*Persea americana*) leaves and fruits	*In vitro,* 0 - 200 µL extracts for enzyme inhibition assay, 0.1 - 0.4 mg/mL for NO scavenging activity	• Inhibition of α-amylase and α-glucosidase activities • Prevention of oxidative stress in the pancreas	Nigeria	2014, [118]
14	Grape seed procyanidin extract	*In vitro* (rat insulinoma INS-1E cells), 25 mg/L	• Enhances the pro-apoptotic effect of high glucose • Shows clear antiproliferative effects under high glucose, insulin and palmitate conditions	Spain	2013, [119]

(Table 2) contd…

No.	Source	Type of study (model), dose and duration	Activity	Origin	Year, [References]
		In vivo (female Wistar rats), 25 and 50 mg of GSPE/kg of body weight for 10 - 30 days	• Modulates pro- and anti-apoptotic markers of the rats pancreas		
15	Ethanolic extract of *Eriobotrya japonica* fruits	*In vivo* (albino rats), 50, 100 and 200 mg/kg body weight for 10 days	• Decreases blood glucose levels significantly and serum lipid profile levels at 200 mg/kg dose	India	2013, [120]
16	Anthocyanin-rich formulation from Maqui Berry (*Aristotelia chilensis*)	*In vitro* (H4IIE hepatoma cells), 20 µg/mL	• Decreases glucose production in the liver and enhance the insulin-stimulated down regulation of the G6Pase	USA	2012, [121]
		In vitro (L6 skeletal muscle cells), 5 - 40 µg/mL	• Increases both insulin and non-insulin mediated glucose uptake		
		In vivo (male C57BL/6J mice), 500 mg/kg	• Improves fasting blood glucose levels and glucose tolerance		
17	Grape seed-derived procyanidins	*In vitro* (human Caco-2 intestinal cells)	• Decreases of DPP-4 activity	Spain	2012, [122]
		In vivo (female Wistar rats), 25 mg/kg body weight daily for 45 days			
18	Wax apple (*Syzygium samarangense)* fruit extract	*In vitro* (mouse liver FL83B cells), 6.25 ng/mL of extract	• Increases expression of IR, IRS-1, Akt/PKB, PI3K and GLUT2 • Increases tyrosyl phosphorylation of IR in insulin resistant conditions	Taiwan	2012, [123]
19	Ethanolic extract of *Terminalia chebula* Retz. fruits	*In vivo* (Wister albino rats), 200 mg/kg body weight/day for 30 days	• Reduces inflammation	India	2012, [124]
20	Juice of Japanese apricot	*In vitro (*mouse 3T3-L1 adipocytes)	• Inhibition of α-glucosidase activity and possesses insulin-like action	Korea	2012, [125]
21	Fruits of *Rubus ellipticus* (Smith)	*In vivo* (Wistar albino rats and Swiss albino mice), 200 mg/kg of petroleum ether, ethanol and aqueous extracts individually	• Three types of extracts exhibit significant antidiabetic effects in both the experimental models of diabetes mellitus	India	2011, [126]
22	Berry fruits of Highbush Blueberry (*Vaccinium corombosum*)	*In vitro* (enzyme inhibitory assay)	• Inhibits α-amylase and α-glucosidase activity	USA	2011, [127]
23	Cambuci (*Campomanesia phaea* Berg.) fruit and cagaita (*Eugenia dysenterica* DC.) pulp	*In vitro*, 40 µL of crude methanolic and polyamide-purified phenolic extract	• Inhibition of α-glucosidase and α-amylase activity	Brazil	2010, [128]
24	Alkaloid-rich dried fruit extract of C*apparis decidua* shrub	*In vivo* (diabetic albino mice), 50 mg/kg body weight daily for 28 days	• Reduces TC and TG content • Attenuates G6Pase, PEPCK, aldose reductase and TNF-α gene expression • Improves GLUT4, PPAR-γ and GK gene expression	India	2010, [129]
25	Aqueous fruits extract of *Diospyros lotus L.*	*In vivo* (male diabetic Wistar albino rats), 500, 750, 1000 and 1500 mg/kg for 16 consecutive days	• Decreases glucose level (maximum effect with 1000 mg/kg dose) • Reduces parenchymal and portal inflammation in liver (1000 mg/kg dose)	Iran	2010, [130]

(Table 2) contd…

No.	Source	Type of study (model), dose and duration	Activity	Origin	Year, [References]
26	Fruit extracts of different strawberry cultivars	*In vitro*	• Honeoye, Idea and Jewel cultivars moderately inhibit α-amylase and ACE • Ovation exhibits the highest α-glucosidase inhibitory activity	USA	2010, [131]
27	Anthocyanin-rich tart cherries (*Prunus cerasus*)	*In vivo* (male Zucker fatty rat model), 90-day treatment	• Reduces hyperlipidemia, retroperitoneal IL-6 and TNF-α expression and plasma IL-6 and TNF-α	USA	2009, [132]
28	Java plum (*Syzygium cumini)* fruit seed (ethyl acetate and methanol extract)	*In vivo* (diabetic Wistar rats), 200 and 400 mg/kg daily for 15 days	• Decreases blood glucose levels	India	2008, [133]
29	Tart cherries	*In vivo (*male Dahl-SS rats), 90 days treatment	• Reduces fasting blood glucose, hyperlipidemia, hyperinsulinemia and fatty liver • Enhances the hepatic PPAR-*α* mRNA and antioxidant capacity	USA	2008, [134]
30	Grape (*Vitis Vinifera)* seed extract and its ethylacetate/ethanol (EE) fractions	*In vivo* (C57BL/KsJ-lepr^{db}/lepr^{db} mice), grape extract (50 mg/kg) and its fractions (each 30 mg/kg) daily for 8 weeks	• Lowers the blood glucose (6-week treatment) and HbA1c level (8-week treatment)	Korea	2009, [135]
31	Ethanolic extract of Canadian lowbush blueberry (*Vaccinium angustifolium* Ait.)fruit	*In vitro* (cell-based bioassays), 12.5 mg/mL	• Protection against glucose toxicity	Canada	2006, [136]
32	Ethanolic extract of *Terminalia chebula* fruits	*In vivo* (adult diabetic male albino rats of Wister strain), 200 mg/kg body weight/day for 30 days	• Reduces blood glucose level and HbA1c • Stimulates insulin action • Normalizes the number of secretory granules of pancreatic β-cells	India	2006, [137]
33	Extract of bitter orange *(Citrus aurantium)* and herb *(Rauwolfia vomitoria)* foliage	*In vivo* (male genetic diabetic inbred C57BL/KsBom-*db* mice), 100 mL/kg body weight/day for 4 weeks	• Induces lipid mobilization from internal stores • Reduces total fatty acid content	Denmark	2006, [138]
34	Fruit juice of *Momordica charantia*	*In vivo* (female Sprague–Dawley rats), 20 mL/kg body weight/day for 27 days	• Reduces blood glucose levels	USA	2006, [139]
35	Plum juice	*In vivo* (obese Wister fatty rats), 2-week treatment	• Decreases blood glucose and plasma TG levels • Increases plasma adiponectin concentrations and PPAR-γ mRNA expression in adipose tissue	Japan	2005, [140]
36	Oxykine (cantaloupe melon extract)	*In vivo* (female diabetic db/db mice), 12-week treatment	• Reduces oxidative stress	Japan	2005, [141]
Vegetables					

(Table 2) contd…

No.	Source	Type of study (model), dose and duration	Activity	Origin	Year, [References]
37	Jicama (*Pachyrhizus erosus*) extract	*In vivo* (male C57BL/Ksj-db/db mice), 0.5 g/100 g of standard semi-synthetic diet for 6 weeks	• Lowers the blood glucose and glycosylated hemoglobin level • Increases insulin sensitivity • Increases phosphorylated AMPK and GLUT4 in skeletal muscle • Decreases G6Pase and PEPCK in the liver	Korea	2016, [142]
38	Polypore mushroom (*Grifola frondosa*)	*In vivo (*male Wistar rats), 1 g/kg/day for 2 weeks	• Decreases postprandial blood glucose • Decreases IFN-γ (T-leukocytes), IL-4, IL-6 (monocytes) and IL-4 (T-splenocytes) production	Taiwan	2015, [143]
39	Cocoa (*Theobroma cacao*) bean	*In vitro* (enzyme inhibition assay), 50 µL of extract	• Inhibition of α-amylase, α-glucosidase and ACE • Dose-dependent free radicals scavenging ability	Nigeria	2014, [144]
40	Jerusalem artichoke (*Helianthus tuberosus*) root extract	*In vivo* (male Wistar rats), 4-week treatment	• Improves insulin resistance • Decreases hepatic TAG accumulation • Alters fatty acid synthesis and inflammation related gene expression	Japan	2014, [145]
41	Extruded adzuki bean protein extract	*In vivo* (male diabetic KK-A^y mice), 42-day treatment	• Decreases the fasting blood glucose level, serum TG, blood urea nitrogen levels • Increases HDL-C	China	2014, [146]
42	Extract of *Grifola frondosa* mushroom	*In vitro* (enzyme inhibition assay), 50 µL of extract	• Inhibition of α-glucosidase activity	Taiwan	2013, [147]
43	Methanolic extract of *Asparagus officinalis* seeds	*In vivo* (diabetic Wistar rats of both sexes), 250 and 500 mg/kg/day for 28 days	• Suppresses blood glucose level • Improves serum insulin levels (500 mg/kg dose) and β-cell function	Pakistan	2012, [148]
		In vitro (DPPH radical-scavenging activity assay)	• Improves the total antioxidant status and show potent antioxidant activity		
44	Lotus root, sesame leaf, bracken, spinach, cucumber, potato, leek, water dropwort	*In vitro (*mouse 3T3-L1 adipocytes)	• Inhibition of α-glucosidase activity and possesses insulin-like action	Korea	2012, [125]
45	Ternatin, a cyclic peptide of mushroom (*Coriolus versicolor*)	*In vivo* (male KK-A^y mice), 8.5 or 17 nmol/day for 4 weeks	• Suppresses hyperglycemia development	Japan	2012, [149]
46	Onion (*Allium cepa* L.)	*In vitro*	• Inhibition of α-glucosidase and α-amylase activity	Korea	2011, [150]
47	ReishiMax extract (contains triterpenes and polysaccharides)	*In vitro* (3T3-L1 preadipocytes), 0 - 300 µg/mL of extract	• Induces AMPK • Increases glucose uptake by adipocytes	USA	2011, [151]

(Table 2) contd…

No.	Source	Type of study (model), dose and duration	Activity	Origin	Year, [References]
	of Ganoderma lucidum mushroom		•		
48	Quercetin-rich onion (*Allium cepa*) peel extract	*In vivo (*male Sprague-Dawley rats), 0.5 or 1% extract for 8 weeks	• Improves glucose tolerance • Increases insulin resistance • Increases expression IR and GLUT4 expression in muscle tissues • Suppresses oxidative stress • Down-regulates inflammatory gene expression in liver	Korea	2011, [152]
49	White button mushroom (*Agaricus bisporus*) powder	*In vivo* (male diabetic Sprague-Dawley rats), 200 mg/kg body weight/day for 3 weeks	• Reduces plasma glucose and TG levels, liver enzyme (AST and ALT) activities	Australia	2010, [153]
50	African vegetables (*Centella asiatica, Ceratotheca triloba, Cleome monophylla, Amaranthus hybridus, Justicia flava, Chenopodium album, Portulaca oleracea)*	*In vitro* (enzyme inhibition assay), 3 and 5 mg/mL	• Inhibition of α-amylase activity	South Africa	2010, [154]
51	Cordycepin (3'-deoxyadenosine) of medicinal mushroom (*Cordyceps militaris*)	*In vitro* [murine macrophages cell line (RAW 264.7)]	• Inhibits NO and pro-inflammatory cytokine (IL-1β, IL-6 and TNF-α) production in activated macrophages	Korea	2009, [155]
52	Phenolic enriched extracts of eggplant (*Solanum melongena*)	*In vitro* (enzyme inhibition assay)	• Possesses free radical scavenging-linked antioxidant activity • Inhibition of α-glucosidase and ACE activity	USA	2008, [156]
53	Fruit body ofmaitake mushrooms (*Grifola frondosa*)	*In vivo* (female diabetic KK-A^y mice), 450 or 150 mg/kg body weight for 2 weeks	• Decreases the body weight, fasting plasma glucose level, GSP, serum insulin, TG, cholesterol, FFA and MDA content in livers • Increases insulin binding capacity to liver crude plasma membranes • Increases insulin sensitivity to IR	China	2007, [157]
54	Exopolysaccharides Of *Tremella fuciformis* and *Phellinus Baumii* mushrooms	*In vivo* (male C57BL/6J ob/ob mice), 200 mg/kg body weight/daily for 52 days	• Reduces the plasma glucose level • Increases the glucose disposal • Increases PPAR-γ mRNA expression in adipose tissue • Improves insulin sensitivity	Korea	2007, [158]

(Table 2) contd…

No.	Source	Type of study (model), dose and duration	Activity	Origin	Year, [References]
Spices					
55	Aridan (*Tetrapleura tetraptera*)	*In vivo* (male Sprague-Dawley diabetic rats), 200 and 400 mg/kg body weight for 28 days	• Protective activity against insulin resistance and anti-inflammatory properties	Cameroon	2015, [159]
56	Ginger (*Zingiber officinal*)	*In vivo* (male Sprague-Dawley diabetic rats), 200 mg/kg/day body weight for 10 weeks	• Protective activity against insulin resistance	Australia	2014, [160]
		In vitro (enzyme inhibition assay)	• Inhibition of α-amylase (IC_{50} = 980.2 µg/mL) and α-glucosidase (IC_{50} = 180.1 µg/mL)	India	2011, [161]
57	Turmeric (*Curcuma longa* L.)	*In vitro* (enzyme inhibition assay)	• Inhibit of α-amylase (IC_{50} = 31.0 µg/mL) and α-glucosidase (IC_{50} = 192 µg/mL)	India	2012, [162]
	Turmeric (*Curcuma longa* L.) volatile oil		• Inhibition of α-amylase (IC_{50} = 24.5 µg/mL) and α-glucosidase (IC_{50} = 0.28 µg/mL)		2012, [163]
	Turmeric (*Curcuma longa* L.)	*In vivo* (female diabetic KK-Ay/Ta mice), 1495 mg/kg/day for 4 weeks	• PPAR-γ activation	Japan	2005, [164]
58	African pepper (*Xylopia aethiopica*), Black pepper (*Piper guineense*), Alligator pepper (*Aframomum melegueta*), African nutmeg (*Monodora myristica*), Bastered melegueta (*Aframomum danielli*), Clove (*Syzygium aromaticum*)	*In vitro* (enzyme inhibition assay)	• Inhibition of α-amylase (IC_{50} = 2.81-4.83 mg/mL) and α-glucosidase (IC_{50} = 2.0-3.5 mg/mL) activity	Nigeria	2012, [165]
	Three varieties of Nigerian peppers (*Capsicum annuum* var. *grossum*, *Capsicum annuum* var. *abbreviatum* and *Capsicum annuum* var. *accuminatum*)	*In vitro* (enzyme inhibition assay)	• Inhibition of α-amylase and α-glucosidase activity	Nigeria	2011, [166]

(Table 2) contd…

No.	Source	Type of study (model), dose and duration	Activity	Origin	Year, [References]
59	Chili (*Capsicum annuum*)	*In vitro* (enzyme inhibition assay)	• Inhibition of α-amylase and α-glucosidase activity	Italy	2011, [167]
	Red chilli (*Capsicum frutescens* L.)	*In vivo* (male Sprague-Dawley diabetic rats)	• Insulinotropic activity	Korea	2008, [168]
60	Garlic (*Allium sativum*)	*In vivo* (male Sprague-Dawley diabetic rats), 500 mg/kg/day for 4 weeks	• Insulinotropic activity	Korea	2008, [169]
Others					
61	Black tea (*Camellia sinensis*) pomace	*In vitro* (enzyme inhibition assay)	• Inhibition of α-glucosidase (IC_{50} = 14.72mg/mL) and α-amylase (IC_{50} = 0.21 mg/mL)	USA	2015, [170]
62	Green tea (*Camellia sinensis*)	*In vivo* (male Balb/c mice), 80 mg/kg weight for 4 weeks	• Decreases blood glucose levels	China	2015, [171]
63	Sesamin (*Sesamum indicum*)	*In vivo* (female KK-Ay mice)	• Hypoglycemic effect by protecting against insulin resistance	China	2013, [172]

HDL-C = High-density lipoprotein cholesterol, TG = Triglyceride, TC = Total cholesterol, FFA = Free fatty acid, AGE = Advanced glycation end-product, MFG-E8 = Milk fat globule epidermal growth factor-8, HOMA-IR = homeostasis model assessment of insulin resistance, DPPH = 2, 2-diphenyl-1-picryl-hydrazyl, HbA1c = Glycosylated hemoglobin, T2DM = Type 2 Diabetes Mellitus, GSIS = Glucose-stimulated insulin secretion, GLUT4 = Glucose transporter 4, GK = Glucokinase, PPAR-γ = Peroxisome proliferator-activated receptor γ, TNF-α = Tumor necrosis factor-α, PEPCK = Phosphoenolpyruvate carboxykinase, NO = Nitric oxide, IRS-1 = Insulin receptor substrate-1, Akt/PKB = Protein kinase B, PI3K = Phosphatidylinositol-3 kinase, GLUT2 = Glucose transporter 2, IR = Insulin receptor, ACE = Angiotensin-1-converting enzyme, DPP-4 = Dipeptidyl Peptidase-4, GLP-1 = Glucagon-like peptide-1, IL-6 = Interleukin-6, GSP = Glycosylated serum protein, MDA = Malondialdehyde, GSHpx = Glutathione peroxidase, ACE = Angiotensin I-converting enzyme, ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, TAG = Triacylglycerol, AMPK = AMP-activated protein kinase, G6Pase = Glucose-6-phosphatase

Table 3. Successful natural products in treating human subjects with T2DM reported between 2005 (January) and 2016 (March).

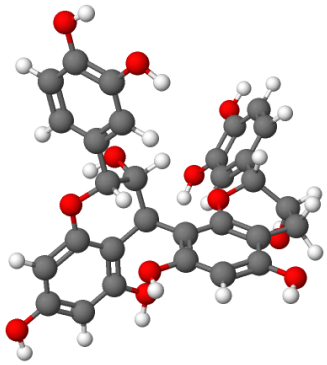
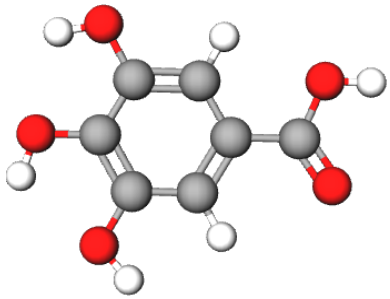
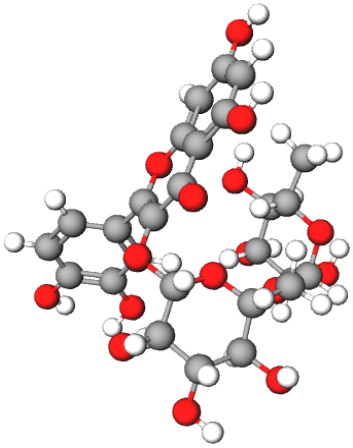
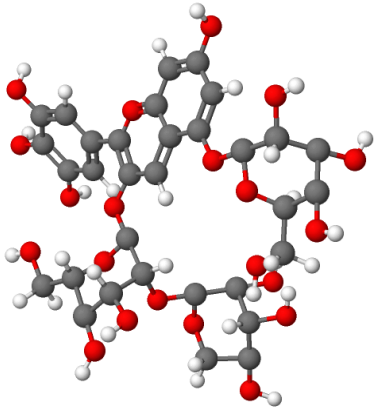
No.	Source	Study Design	Consumption status	Outcome	Origin	Year, [References]
1	Coffee (*Coffea arabica*)	Observational study	≥ 3 times/day, 3.7 ± 2.3 years	Drinking coffee (without sugar and creamer) at least three times daily has significant (p = 0.036) preventive effects on diabetes onset	Korea	2016, [173]
2	Blend of sesame and rice bran oil	OLRDI	8 weeks	Significant reduction ($p < 0.001$) of fasting and post prandial blood glucose	India	2016, [174]
3	Ginger (*Zingiber officinale*)	RCT	3 g/day, 3 months	Significant improvement ($p < 0.001$) in lowering blood glucose, HbA1c, insulin activity and lowering insulin resistance	Iran	2015, [175]
4	Turmeric (*Curcuma longa* L.)	RCT	2 g/day, 4 weeks	Significant reduction in lipid peroxidation ($p < 0.05$) and enhancement of total antioxidant status ($p < 0.05$).	India	2015, [176]
		CT	6 g	Significant improvement (p = 0.03) in postprandial serum insulin levels	Sweden	2010, [177]

(Table 3) contd…

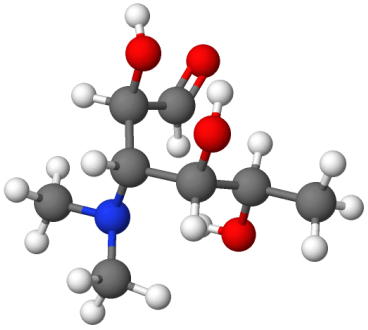
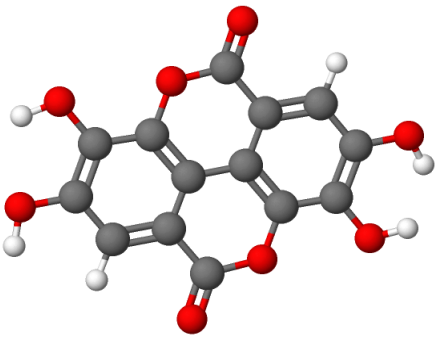
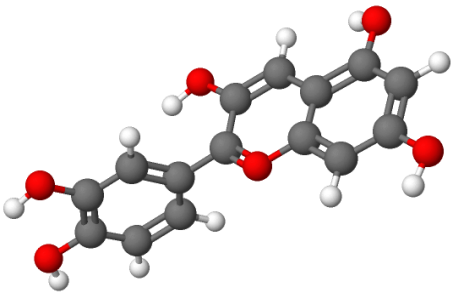
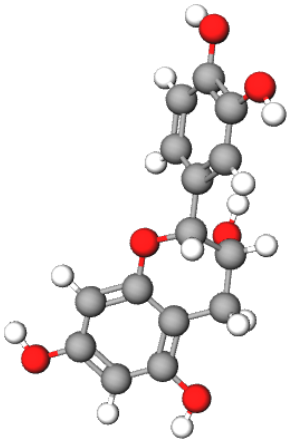
No.	Source	Study Design	Consumption status	Outcome	Origin	Year, [References]
5	Grape (*Vitis vinifera*)	Intervention study	8 mg,12 months	Down-regulating expression of key pro-inflammatory cytokines provides a beneficial effect on T2DM	Spain	2014, [178]
6	Ginger (*Zingiber officinale*)	RCT	1.6 g/day, 12 weeks	Improves insulin sensitivity	Iran	2014, [179]
			3 g/day, 8 weeks	Fasting blood glucose and HbA1c concentration were reduced significantly ($p = 0.003$)		2014, [180]
			2 g/day, 12 weeks	Fasting blood glucose and HbA1c concentration were reduced significantly ($p < 0.001$)		2013, [181]
7	Wine	Prospective study	0.81 drinks/day (1 drink = 150 mL)	Moderate wine consumption throughout life for overweight women has a beneficial effect against T2DM	France	2014, [182]
	Red wine	Observational study	360 mL/day, 2 weeks	Attenuates insulin resistance in T2DM patients without affecting vascular reactivity	Italy	2005, [183]
8	Green tea (*Camellia sinensis*)	RCT	150 mL, 3 times/day, 4 weeks	Exerts positive effects on insulin resistance	Iran	2014, [184]
			500 mg green tea extract thrice/day, 16 weeks	Significantly improves insulin resistance and increase GLP-1	Taiwan	2014, [185]
9	Pistachio nut (*Pistacia vera*)	RCT	25 g twice/day, 12 weeks	Beneficial effects on glycemic control	Iran	2013, [186]
10	Walnut (*Juglans regia*)	Prospective study	1 - 3 servings/month (1 serving = 28 g)	Inversely associates ($p < 0.001$) with the risk of T2DM	USA	2013, [187]
11	Broccoli sprout (*Brassica oleracea* var. *italica*)	RCT	10 g/day, 4 weeks	Potential in improving insulin resistance ($p < 0.05$)	Iran	2012, [188]
				Attenuates oxidative stress and imposes favorable effects on T2DM patients		2011, [189]
12	Beans (Pinto, dark red kidney and black beans) with rice	Cross-over study	50 g	Pinto beans/rice ($p = 0.011$), black beans/rice ($p = 0.004$) and red kidney beans/rice ($p = 0.040$) significantly lower the postprandial net glucose values	USA	2012, [190]
13	Sesame (*Sesamum indicum*) oil	OLRDI	35 g/day, 60 days	Exhibits a synergistic effect with glibenclamide	India	2011, [62]
14	Red onion (*Allium cepa*)	Observational study	100 g, 4 hours	Able to produce hypoglycemic effect	Sudan	2010, [191]
15	Mushroom (*Agaricus blazei* Murill)	Prospective study	1.5 g/day, 12 weeks	Improves insulin resistance significantly ($p < 0.04$)	Taiwan	2007, [192]
16	Muscadine grape wine and dealcoholized muscadine grape wine	Observational study	150 mL/day, 28 days	Increases insulin sensitivity and decreases tendency towards impaired liver function	USA	2006, [193]

RCT = Randomized controlled trial; OLRDI = Open label randomized dietary intervention; CT = Crossover trial, GLP-1 = Glucagon-like peptide-1, T2DM = Type 2 diabetes Mellitus, HbA1c = Glycated hemoglobin

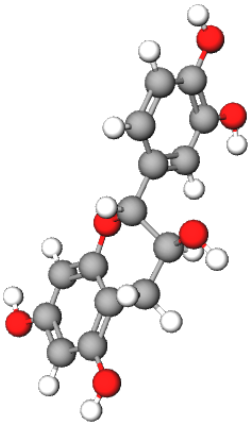
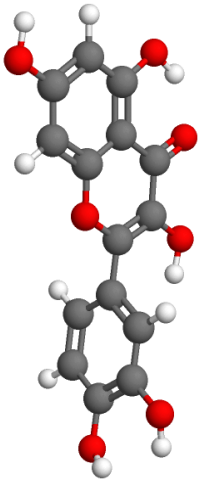
Table 4. Some potential antidiabetic active compounds from natural products reported between 2005 (January) and 2016 (March).

No.	Active compounds	Structure	Sources	References
		Fruits		
1	Procyanidin B2		• Grape (*Vitis vinifera*)	[112]
2	Gallic acid		• Sweet granadilla (*Passiflora ligularis*)	[115]
	Rutin			
3	Delphinidin 3-sambubioside-5-glucoside		• Maqui Berry (*Aristotelia chilensis*)	[121]

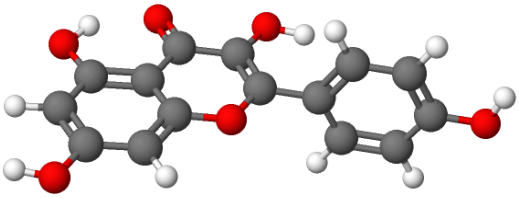
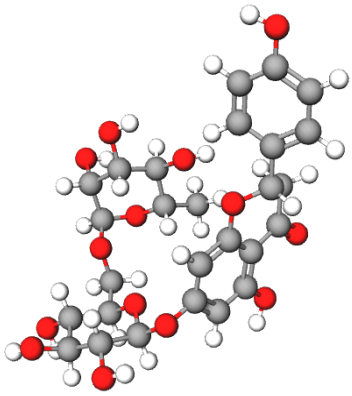
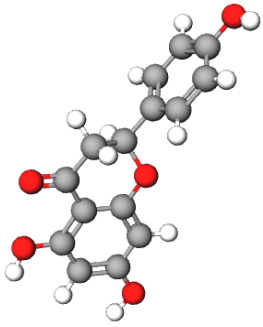
(Table 4) contd….

No.	Active compounds	Structure	Sources	References
4	Mycaminose		• Java Plum (*Syzygium cumini*)	[133]
5	Ellagic acid		• Brazil plum (*Spondias tuberosa* Arruda) • Camu camu (*Myrciaria dubia* Mc. Vaugh) • Cagaita (*Eugenia dysenterica* DC.) • Acaçá (*Psidium guineensis* Sw.) • Cambuci (*Campomanesia phaea* Berg.)	[128]
6	Cyanidin		• Camu camu (*Myrciaria dubia* Mc. Vaugh)	
7	Epicatechin		• Star fruit (*Averrhoa carambola*) • Graviola (*Annona muricata* L.)	

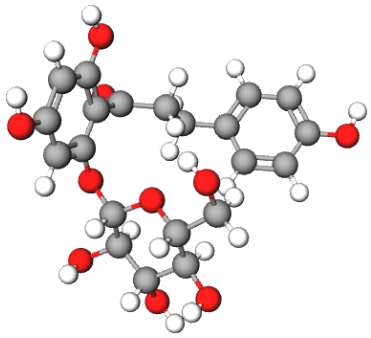
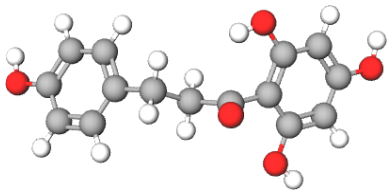
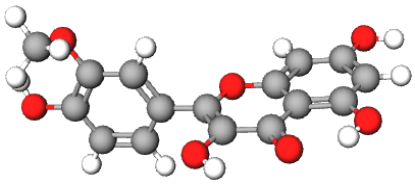
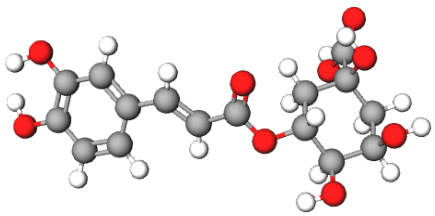
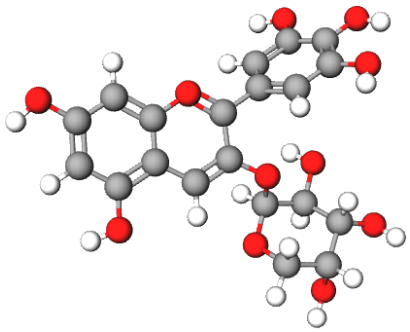
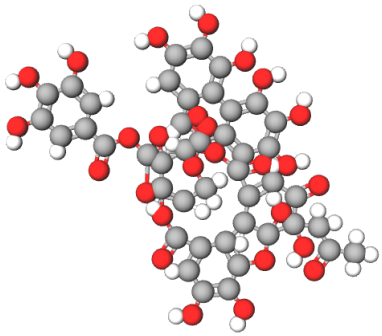
(Table 4) contd….

No.	Active compounds	Structure	Sources	References
	Catechin			
8	Quercetin		• Cambuci (*Campomanesia phaea* Berg.) • Araza (*Eugenia stipitata* Mc. Vaugh) • Camu camu (*Myrciaria dubia* Mc. Vaugh) • Acaçá (*Psidium guineensis* Sw.) • Tucumã (*Astrocaryum aculeatum*) • Buriti (*Mauritia flexuosa*) • Brazil plum (*Spondias tuberosa* Arruda) • Panã (*Annona crassifolia* Mart.) • Cagaita (*Eugenia dysenterica* DC.)	

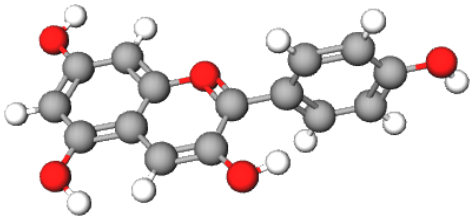
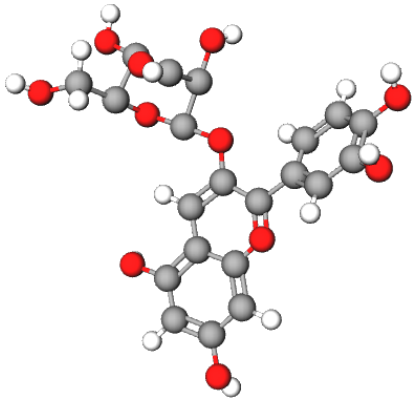
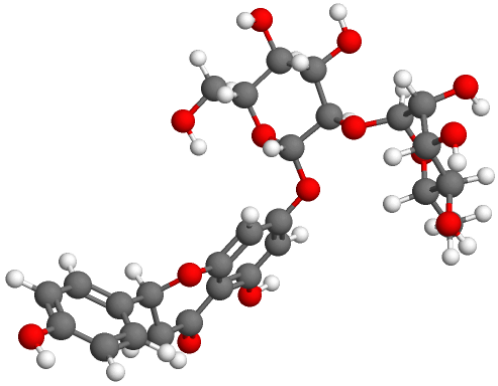
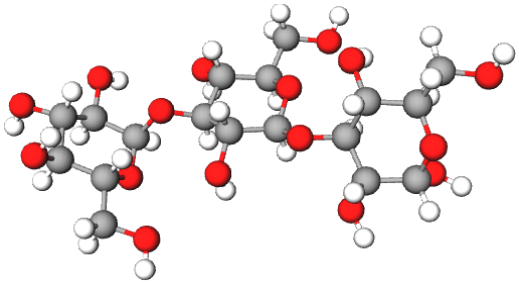
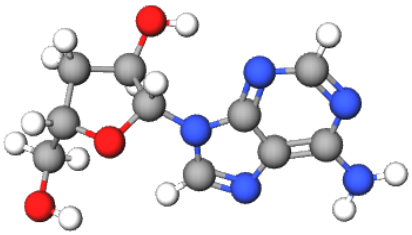
(Table 4) contd….

No.	Active compounds	Structure	Sources	References
9	Kaempferol		• Cambuci (*Campomanesia phaea* Berg.) • Araza (*Eugenia stipitata* Mc. Vaugh) • Acaçá (Psidium guineensis Sw.) • Panã (Annona crassifolia Mart.) • Cagaita (*Eugenia dysenterica* DC.)	
10	Naringenin-7-o-rutinoside		• Grapefruit (*Citrus* x *paradisi*)	[116]
	Kaempferol-3-o-rutinoside			
	Naringenin			

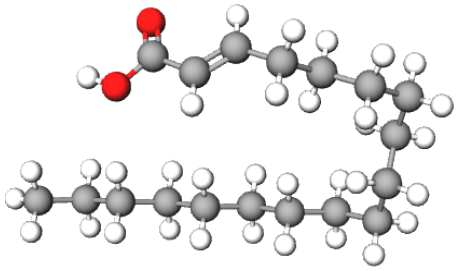
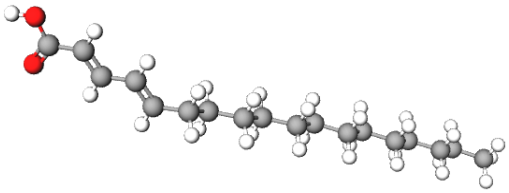
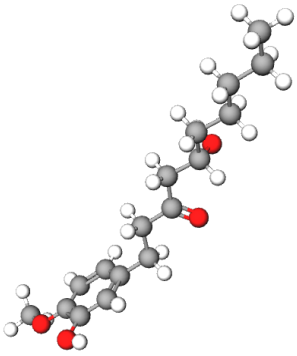
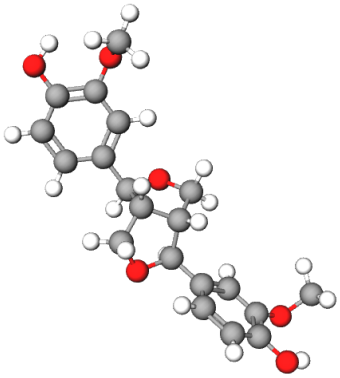
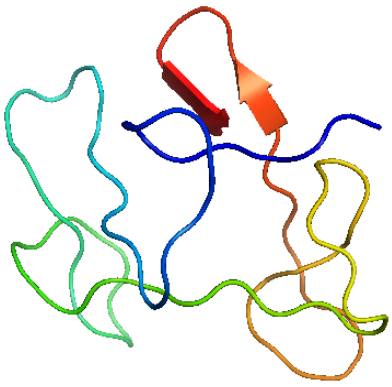
(Table 4) contd….

No.	Active compounds	Structure	Sources	References
11	Phlorizin		• Apple (*Malus domestica* Borkh.)	[117]
	Phloretin			
	Isorhamnetin			
	Chlorogenic acid			
12	Delphinidin-3-arabinoside		• Blackberry (*Rubus fruticosus*)	[108]
13	Ellagitannin		• Strawberry (*Fragaria* x *ananassa* Duch.)	[194]

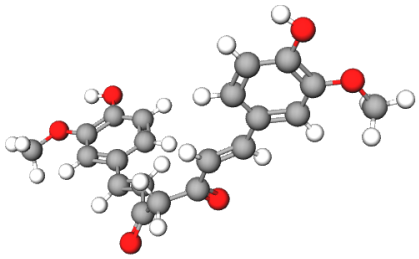
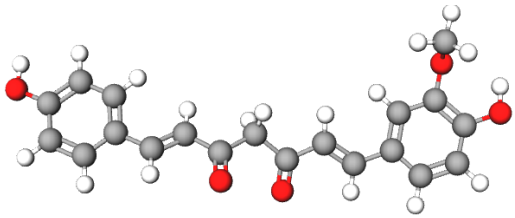
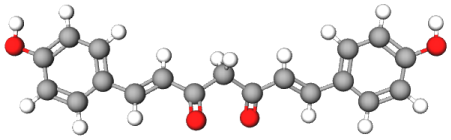
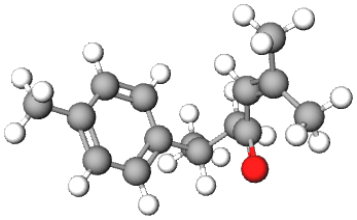
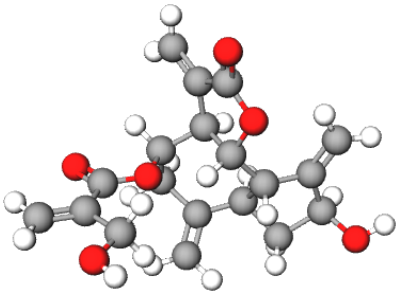
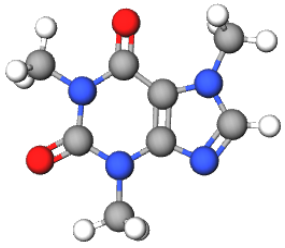
(Table 4) contd….

No.	Active compounds	Structure	Sources	References
14	Pelargonidin		• Bilberry (*Vaccinium myrtillus*)	[195]
	Cyanidin 3-glucoside			
15	Naringin		• Orange (*Citrus* x *sinensis*)	[196]
Vegetables				
16	α-glucan		• Polypore mushroom (*Grifola frondosa*)	[157]
17	Cordycepin (3'-deoxyadenosine)		• Medicinal mushroom (*Cordyceps militaris*)	[155]

(Table 4) contd….

No.	Active compounds	Structure	Sources	References
18	7(Z)-octadecenoic acid		• Sea Cucumber (*Stichopus japonicus*)	[197]
	7(Z),10(Z)-octadecadienoic acid			
Spices				
19	(S)-(6)-gingerol		• Ginger (*Zingiber officinale*)	[160]
20	(+)-Pinoresinol		• Sesame (*Sesamum indicum*)	[198]
21	Turmerin		• Turmeric (*Curcuma longa* L.)	[162]

(Table 4) contd….

No.	Active compounds	Structure	Sources	References
22	Curcumin			[199]
	Demethoxycurcumin			
	Bisdemethoxycurcumin			
	ar-turmerone			
23	Curcuminoids			[164]
	Sesquiterpenoids			
Others				
24	Caffeine		• Green tea (*Camellia sinensis*)	[171]

leeks **OR** mushrooms **OR** onion **OR** okra **OR** pea pods **OR** peppers **OR** radish **OR** pepper **OR** black pepper **OR** red chills **OR** green chili **OR** rutabaga **OR** chicory **OR** escarole **OR** endive **OR** lettuce **OR** romaine **OR** arugula **OR** tomatoes **OR** Swiss chard **OR** spinach **OR** watercress **OR** turnip **OR** mustard **OR** collard **OR** sprouts **OR** radicchio **OR** peas **OR** turnips **OR** vegetables **OR** yard-long beans **OR**) **AND** (type 2 diabetes mellitus **OR** T2DM **OR** non-insulin dependent diabetes mellitus **OR** type 2 diabetes **OR** type 2 diabetic)]

Spices

[(adobo seasoning **OR** allspice **OR** anise seed **OR** apple pie spice **OR** bay leaf **OR** cardamom seed **OR** cayenne **OR** chili peppers **OR** cinnamon **OR** cloves **OR** cumin **OR** curry powder **OR** fennel seed **OR** fenugreek seed **OR** five spice **OR** garam masala **OR** garlic & herb seasoning **OR** ginger **OR** mace **OR** mustard **OR** nutmeg **OR** onion **OR** paprika **OR** peppercorns **OR** saffron **OR** sesame **OR** spice **OR** star anise **OR** thyme leaf **OR** turmeric) **AND** (type 2 diabetes mellitus **OR** T2DM **OR** non-insulin dependent diabetes mellitus **OR** type 2 diabetes **OR** type 2 diabetic)]

Others

[(Nuts **OR** mushroom **OR** green tea **OR** black tea **OR** coffee **OR** wine) **AND** (type 2 diabetes mellitus **OR** T2DM **OR** non-insulin dependent diabetes mellitus **OR** type 2 diabetes **OR** type 2 diabetic)]

SYNERGISTIC INTERACTION BETWEEN ANTIDIABETIC DRUGS WITH NATURAL PRODUCTS

Presently, T2DM cannot be adequately treated using currently available antidiabetic drugs, particularly when the disease has progressed to an advanced stage. Therefore, in this review, the possibility of treating T2DM with a novel combination between natural products and common antidiabetic drugs is explored. The complicated pathogenesis of diabetes provides an avenue for combination therapy between modern therapy and natural products to make these treatments more effective in treating this disease. Synergistic effects may also occur, which may be helpful in reducing the dose of antidiabetic drugs in the treatment of T2DM while minimizing adverse effects related to the drugs.

Metformin

In alloxan-induced diabetic mice, the concomitant administration of the aqueous extract of oyster mushroom *(Pleurotus pulmonarius)* at dose of 500 mg/kg with metformin (250 and 500 mg/kg) and piperine alkaloid (10 mg/kg) from the fruit extract of black pepper (*Piper nigrum*) with metformin (125 and 250 mg/kg) synergistically interact ($p < 0.001$ and $p < 0.05$, respectively) to significantly potentiate the antihyperglycemic activity by lowing the blood glucose level and body weight compared to metformin alone [38, 39]. In normal albino rabbits, the ethanolic extract of bael fruit (*Aegle marmelos*) at a dose of 250 mg/kg in combination with metformin (11.16 mg/kg) enhanced its effect and prolonged its therapeutic value [40]. The administration of garlic (*Allium sativum*) extract at a dose of 500 mg/kg and the administration of bitter gourd fruit juice *(Momordica chrantia)* at a dose of 20 mL/kg synergistically as well as significantly ($p < 0.01$) potentiated the hypoglycemic effect of metformin (50 and 100mg/kg) by reducing the blood glucose level in streptozotocin (STZ)-induced diabetic Wistar rats [41, 42]. At a dose of 250 mg/kg, oleanolic acid, which can be found in many natural products including garlic, olive oil and java apple, showed synergistic effects in combination with metformin (100 mg/kg) by significantly reducing blood glucose and insulin levels, improving liver pathology, significantly increasing the mRNA expression of glycogen synthesis and decreasing the glycogen phosphorylase, PGC-1α, PEPCK1 (phosphoenolpyruvate carboxykinase 1), and G6Pase levels in a db/db (male C57BL/KsJ-Lepdb) diabetic mouse model**.** The enhanced phosphorylation of AMPK (adenosine monophosphate-activated protein kinase) and AKT and the enhancement of the reduced expression of proteins and genes relevant to glucose metabolism were also observed. Thus, the combination therapy of natural products with modern drugs can succeed in controlling hypoglycemia by decreasing both gluconeogenesis and glycogenolysis and hepatic glucose production, which is beneficial for the treatment of T2DM [43]. The co−administration of *Cassia auriculata* L. leaf extract (500 mg/kg) with metformin (45 and 90 mg/kg) showed a synergistic herb‑drug interaction in STZ-induced diabetic Wistar rats [44]. The ethanol extract of *Moringa oleifera* leaves (100 - 2000 mg/kg) along with metformin (150 mg/kg) showed greater ($p < 0.001$) antihyperglycemic and hypolipidemic effects in diabetic Wistar rats, which may be useful in the therapeutic management of T2DM associated with dyslipidemia [45]. The aqueous extract of *Trichosanthes dioica* leaves (800 mg/kg) concomitantly administered with metformin (250 and 500 mg/kg) significantly ($p < 0.05$) enhanced the antihyperglycemic effect of metformin in STZ-induced diabetic Wistar rats, which may exploited for better

management of diabetic patients [46]. These combination approaches could be used as adjuvants for managing hyperglycemia and prolonging metformin action in T2DM patients who are already taking metformin.

Pioglitazone

In high fat diet and STZ-induced male Sprague-Dawley rats, the combination treatment of omega-3 fatty acids (10% W/W diet) with pioglitazone (20 mg/kg) for 4 weeks significantly decreased FGF21 (fibroblast growth factor 21) concentrations in the serum and liver, improved the lipid profile and insulin resistance and decreased blood glucose levels [47]. In the L6 myoblast cell line, ellagic acid from the methanol extract of pomegranate *(Punica granatum* L.*)* peels synergistically interacted with pioglitazone to increase insulin stimulated glucose uptake. Pioglitazone activates peroxisome proliferator-activated receptor γ (PPAR-γ) to up-regulate adiponectin which was enhanced at lower concentrations of the drug after combining with pure ellagic acid. Insulin sensitizing activity by pioglitazone was also enhanced at low doses in combination with ellagic acid [48]. In alloxan monohydrate-induced female Wistar rats, pioglitazone (10 mg/kg) in combination with curcumin from turmeric (*Curcuma longa*) at 60 mg/kg dose was applied. Curcumin effectively improved the pharmacodynamics (glycemic control) which indicated that the alteration might be partly because of the improved pharmacokinetics of pioglitazone and partly because of the antihyperglycemic activity of curcumin [49]. In alloxan monohydrate-induced male albino Wistar rats, the ethanolic extract of *Piper cubeba* Linn. fruits (400 mg/kg) enhanced pioglitazone (10 mg/kg) activity and significantly lowered blood glucose levels in the combinational treatment group compared to pioglitazone alone [50]. The co-administration of pioglitazone (10 mg/kg) and *Cassia auriculata* (450 mg/kg) in the ratio of 25:75 in alloxan monohydrate-induced diabetic rats for 28 days restored the levels of renal, cardiac and hepatic parameters compared to a 100% dose (10 mg/kg) of pioglitazone [51]. A similar study also found that this combination ameliorated free radical mediated oxidative stress [52].

Acarbose

In an *in vitro* study, combination of green tea extracts, green tea polyphenols or epigallocatechin gallate (EGCG) with acarbose at low concentrations synergistically inhibited α-amylase and α-glucosidase enzymes activity [53]. Extracts of both black currant (composed of ~70% anthocyanins) and rowanberry (composed of ~65% chlorogenic acids) synergistically potentiated the inhibition of α-glucosidase activity *in vitro* mediated by acarbose. These extracts could substitute the potential of acarbose or could help to reduce the acarbose dose [54]. In alloxan monohydrate-induced diabetic Swiss albino mice, treatment (28 days) with the aqueous extract of mushroom (*Pleurotus pulmonarius*) at a dose of 500 mg/kg produced a more synergistic significant ($p < 0.001$) antihyperglycemic effect in combination with acarbose (50 mg/kg) than the drug alone [55]. A low dose of cyanidin-3-galactoside (a natural anthocyanin) synergistically inhibited the intestinal α-glucosidase (maltase and sucrase) enzyme in combination with acarbose *in vitro* [56]. The combination of acarbose with cyandin-3-rutinoside (C-3-R) produced a significant additive inhibitory effect against pancreatic α-amylase *in vitro* [57]. The synergistic inhibition of C-3-R against intestinal maltase and sucrase *in vitro* was also found in combination with acarbose. Moreover, the oral administration of C-3-R (30 mg/kg) with acarbose to normal rats markedly reduced the postprandial plasma glucose compared to acarbose alone through the inhibition of intestinal α-glucosidase [58]. The combination of cyandin-3-glucoside, cyanidin-3-galactoside or cyanidin-3,5-diglucosides synergistically inhibited intestinal maltase and sucrase with a low concentration of acarbose [59].

Glibenclamide

In diabetic male albino Sprague-Dawley rats, treatment with glibenclamide (6 mg/kg) along with curcumin (50 mg/kg) significantly increased the half-life and mean residence time of glibenclamide compared to glibenclamide alone, which revealed that curcumin has a potential inhibitory effect on intestinal CYP3A4 in the intestine and liver (an isozyme responsible for glibenclamide metabolism), thus decreasing glibenclamide metabolism [60]. In STZ-induced diabetic rats, oral glibenclamide at two different doses of 0.25 and 0.5 mg/kg and garlic extract (500 mg/kg) produced a greater hypoglycemic effect as a combination than either of the compounds alone. This study concluded that garlic extract could be used synergistically with glibenclamide to reduce its dose to achieve an enhanced therapeutic effect with minimal side-effects [61]. In an open label on T2DM patients, the combination of sesame oil (35 g of oil/day/person) and glibenclamide (5 mg/day, single dose) improved the anti-hyperglycemic effect with a 36% reduction of glucose, a 43% reduction of HbA1c, and reductions of TC (total cholesterol), LDL-C (low-density lipoprotein cholesterol) and TG

(triglyceride) levels with improved HDL-C (high-density lipoprotein cholesterol) levels in the plasma. The synergistic effect of sesame oil could be a safe and effective choice for combination treatment with glibenclamide in clinical practice for combating hyperglycemia [62]. Treatment with unripe fruit juice (20 mL/kg) of *Momordica charantia* in STZ-induced diabetic rats along with glibenclamide (orally, 0.25 and 0.50 mg/kg) synergistically produced a hypoglycemic effect, which is thought to be important in reducing the glibenclamide dose for T2DM treatment [63]. The methanolic extract administration of *Ficus glomerata* Roxb. bark (200 mg/kg) in Swiss albino diabetic rats in combination with glibenclamide (300 and 600 μg/kg) showed a significant ($p < 0.01$) hypoglycemic effect compared to their individual treatments. This beneficial synergistic effect of herb-drug interaction could provide an opportunity to reduce the dose of glibenclamide [64]. Similar results were obtained from the synergistic interaction between glibenclamide (300 and 600 μg/kg) and the methanolic extract of bark of *Pongamia glabra* Vent. (200 mg/kg) when applied in alloxan monohydrate-induced diabetic rats [65].

Gliclazide

In STZ-induced diabetic adult male Wistar albino rats, the oral administration of garlic extract (10 mL/kg) combined with gliclazide (1 mg/kg) produced a significant ($p < 0.05$) antidiabetic effect compared to their single administrations [66]. Similar results were obtained with the oral administration of carrot juice (10 mL/kg) in combination with 1 mg/kg of gliclazide [67]. The oral treatment of alloxan monohydrate-induced diabetic albino rats with the methanolic *Syzygium cumini* seeds extract (500 mg/kg) produced antidiabetic activity when administered alone but prolonged effects of gliclazide (2 mg/kg) when used in combination in both normal and diabetic rats with no hypoglycemic convulsions. The blood glucose levels of gliclazide were not altered because of the presence of the seed extract. The study noted that the combination can be safely used to yield an extended and persistent antidiabetic effect [68]. In albino Wistar rats, the oral administration of the ethanolic extract of aerial parts of *Andrographis paniculata* (2 gm/kg) for 7 days followed by gliclazide (2 mg/kg) on the 8th day increased the bioavailability (63.39%) of gliclazide, which suggests the decreased metabolism of gliclazide by *Andrographis paniculata* involving CYP2C9 and CYP3A4 enzymes. Thus, *A. paniculata* extract should be cautiously used, and the dose of gliclazide must be optimized when concomitantly administered to minimize the adverse effects of gliclazide [69]. The oral administration of the aqueous extracts of the entire plant of *Tinospora cordifolia* (200 mg/kg) followed by gliclazide administration (2 mg/kg, orally) in albino Wistar rats significantly increased the hypoglycemic and antihyperglycemic activities of gliclazide [70]. In alloxan monohydrate-induced diabetic albino rats, the oral administration of the aqueous leaf extract of *Azadirachta indica* (30 mg/kg) with gliclazide (5.6 mg/kg) did not alter the pharmacokinetics of gliclazide in rabbits, indicating that the combination of gliclazide and *A. indica* can be used safely to obtain elongated and sustained antidiabetic effects [71]. Similar observations were obtained from the interaction between the extract of *Trigonella foenum-graecum* (fenugreek) seed powder (30 mg/kg) and the gliclazide (5.6 mg/kg) [72]. In STZ-induced diabetic albino rats, the effect of the *Gymnema sylvestre* (500 mg/kg) on the pharmacokinetics and pharmacodynamics of gliclazide (20 and 40 mg/kg) was investigated. In this study, the bioavailability of gliclazide decreased with increased clearance and increased the volume of pancreatic islets cells. *G. sylvestre* negatively influenced the pharmacokinetics but positively influenced the pharmacodynamics of gliclazide [73]. Another *in vivo* study on alloxan monohydrate-induced diabetic Wistar albino rats evaluated the interaction of the aqueous extracts of the entire *G. sylvestre* plant (100 mg/kg) with gliclazide (2 mg/kg) and a found synergistic interaction between them with a significant increase in the hypoglycemic and antihyperglycemic activity of gliclazide potentiated by *G. sylvestre* [74].

Glimepiride

In STZ-induced male albino Wistar rats, the combination of glimepiride (1 mg/kg) with curcumin (80 mg/kg) delivered significant protective effects against diabetes-mediated changes in the biochemical parameters, improved the total antioxidant status, and enhanced the glimepiride bioavailability through the inhibition of the CYP2C9 enzyme, which led to the suggestion that curcumin might be advantageous as an adjuvant to glimepiride in a proper dose for T2DM treatment [75]. Similar results were obtained from another in *vivo* study in which glimepiride (1 mg/kg) was used in combination with piperine (20 mg/kg) [76]. In STZ and nicotinamide-induced male Wistar albino rats, a significant ($p < 0.05$) hypoglycemic and anti-hyperlipidemic effect was observed with the co-administration of glimepiride (1 mg/kg) and garlic (250 and 500 mg/kg) compared to glimepiride alone. In this study, glimepiride treatment along with garlic not only suc-

ceeded in tightening the glycemic control but also provided beneficial hypolipidemic changes, closely related to T2DM progression [77]. A synergistic interaction between the aqueous extract of *Ocimum sanctum* leaf (100, 200 and 400 mg/kg) and glimepiride (0.036, 0.072 and 0.144 mg/200 g, orally) in STZ-induced diabetic albino mice was observed when applied in combination with significant antidiabetic activity compared to either of the drugs given alone [78].

PROPOSED SAFETY CONCERNS FOR T2DM MANAGEMENT

Prior to the use of natural products in T2DM patients, understanding their safe use can help reduce the possible risk of drug interactions and maximize their therapeutic efficacy. Some safety issues are proposed below that should be considered prior to the initiation of combination treatment with drug and natural products so that patients' safety is maximized with negligible side-effects:

1) The selection of the therapeutic dose is necessary for the proper management of T2DM. Both natural products and pharmaceutical drugs can be therapeutically advantageous at one dose whereas they may cause adverse reactions at another dose. Interactions between natural products and oral hypoglycemic drugs may potentiate or reduce the pharmacological or toxicological effects of either component. Synergistic therapeutic effects may complicate the dosing of long-term medications. For example, natural products, which can decrease blood glucose levels in T2DM, could potentially lead to severe hypoglycemia if taken in combination with oral hypoglycemic drugs. Therefore, caution should be taken when combining any oral hypoglycemic drug with natural products.

2) Because there is growing interest regarding the potential benefits of natural products for T2DM treatment, it is very important to monitor the advancement of the clinical literature and to share these findings with T2DM patients. Until more authoritative studies explain specific interactions between oral hypoglycemic drugs and natural products, clinicians should remain thoughtful about the dose, application technique, efficacy, complications and contradictions to provide a more secure and successful practice and to properly inform their patients; simultaneously, they must be liberal regarding the adjunctive use of these products. They should not make decisions based on only sound clinical judgment; rather, they should also consider the patients' comfort, requirements and priorities. Apart from this, a framework is necessary to develop medical system that is capable of incorporating complementary therapies that have been confirmed to be beneficial for T2DM management. Further studies are necessary to substantiate the observation of natural products and drug interactions and to elucidate the active principles and exact mechanisms of action involved in the antidiabetic activity of natural products.

3) Numerous risk factors such as life-style related factors, acquired factors, and genetic and epigenetic factors can enhance the possibility of adverse effects during the simultaneous use of natural products and standard regimens. Therefore, these factors should be cautiously scrutinized as part of a risk/benefit analysis before beginning a treatment regimen, during a dose selection or dose change or following the withdrawal of a complementary treatment in T2DM patients.

4) Many patients begin a new treatment regimen made of natural products without physician knowledge. However, it is important to consult and provide the right information about diet and medication to the physician, who may be able to guide the correct treatment strategy with proper adjustment of dose and to monitor the reactions in response to the therapies.

TYPICAL DRUG DEVELOPMENT AND APPROVAL PROCESS

Although drug discovery from natural products is a challenging and lengthy task, active compounds from natural products are expected to remain vital components in the quest of novel drugs. Pre-clinical research beginning from lead identification (screening through bioassays such as target-based bioassays, cell-based bioassays and *in vivo* bioassays) from natural products is the first step in the drug discovery process. Thereafter, lead isolation, lead optimization and the lead development process [using pharmacology, toxicology, pharmacokinetics, ADME (absorption, distribution, metabolism and excretion) and drug delivery] are continued step by step [79]. The drug candidate is then tested *in vitro* and *in vivo* using animal models. An application on the Investigational New Drug (IND) is

submitted to the Food and Drug Administration (FDA) before proceeding to clinical trials (phases I, II and III). In phase I, safety and dosage of the drug candidate is determined in healthy volunteers (n = 20-100). In phase II, efficacy and side-effects are determined in patients (n = 100-300). In phase III, assessment of efficacy and monitoring of adverse reactions are carried out in patients (n = 1000-2000). Following the successful completion of clinical trials, a New Drug Application (NDA) in the US or a Marketing Authorization Application (MAA) in Europe is submitted to seek approval for initiating the marketing of the drug [80] (Fig. **2**).

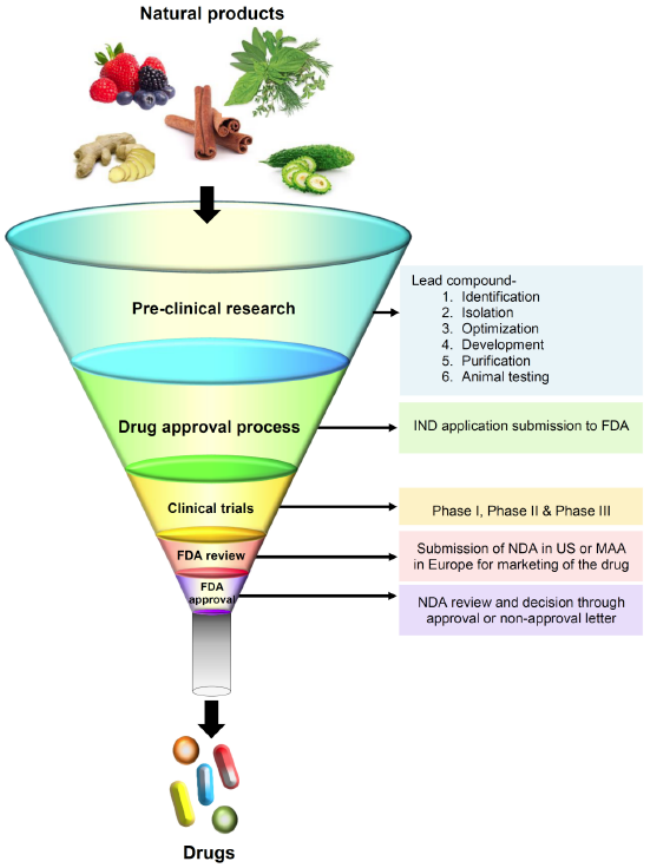


Fig. (2). Funnel diagram showing the sequential stages of natural product-derived drug development and the drug approval procedure.

CHALLENGES AND SOLUTIONS IN DRUG DISCOVERY FROM NATURAL PRODUCTS

Pharmacognocists, phytochemists and other related scientists who work with natural products must be constantly devoted for the improvement of the quality and quantity of compounds that enter the drug development process to maintain speed with other drug discovery efforts [81]. But the pharmacy departments in academic institutions mainly focus on the production of clinical and community pharmacists rather than emphasizing on pharmaceutical research and drug discovery from natural products. So the drug discovery from natural product is declining. However, several initiatives have been taken to reverse this tendency in the USA via the establishment and development of the National Center for Natural Products Research at the University of Mississippi, the National Institutes of Health (NIH) Botanical Centers at the University of Illinois at Chicago and the University of Arizona and the establishment of an endowed chair in natural products chemistry and pharmacognosy at The Ohio State University [79].

The approximate estimated time for the complete drug discovery process is 10 years or longer [82], which may cost in excess of 800 million dollars [83]. The majority of this time and money is paid on the exploration of numerous leads that are usually excluded during the processing period; in fact, only one in 5000 lead compounds successfully enters into the drug development cycle and receives FDA final approval for use. Because of the lengthy time requirements and many complications for drug discovery from natural products, many pharmaceutical companies have removed or scaled down their natural product research [81, 84]. Because drug development from natural compounds or plants is very time-consuming, faster and more advanced approaches for natural product collection, screening through bioassays, isolation and development of the lead compound are necessary to reduce the time [84, 85]. Innovative and advanced strategies are required to improve the natural compound collection process, particularly regarding the legal and political issues surrounding benefit-sharing agreements [86]. Clinically relevant high-throughput bioassays are a challenging task in terms of design, determination and implementation for the lead identification/screening process in drug discovery. However, once the design of high-throughput screening assays is successfully performed, lead compound and extract libraries can be tested further for biological activity [87]. The problems associated with the screening of extract libraries can be alleviated through using prefractionation techniques for extracts [81, 84]. After lead identification, the isolation of the lead compound is another difficult issue. However, new technologies are now being incorporated to speed up this process. Nuclear magnetic resonance (NMR) and mass spectrometry (MS) techniques are now widely used for facilitating lead compound identification and isolation [88, 89]. High-throughput X-ray crystallography can also be useful for lead discovery from natural products [90]. The optimization and development of a drug's lead compound after its discovery from natural products is another challenging issue.

The lead compound is typically obtained in insignificant amounts following isolation from the natural product, which is insufficient for lead optimization and development and for clinical trials. In this case, synthetic and medicinal chemists may determine the possibility of conducting a synthesis or semi-synthesis process [91, 92]. The chemical synthesis of the lead compound may occur by mimicking the similar active structures present in the natural products following confirmation of their structural conformations and configurations to obtain significant amounts of the lead compound [93]. Additionally, the formation of natural product and natural-product-like libraries through chemistry and combinatorial chemistry can be adopted to improve the development of lead compounds [84, 94, 95].

Drug testing on animals is not an ideal option because these tests limit the predictive value of metabolic dissimilarities between humans and animals. Many ethical issues are also raised by such testing. To replace animal testing, microfluidic devices integrated with two or more cell types either in two-dimensional or three-dimensional cell cultures is currently being used. These devices simulate different human organs on a single chip [96, 97], which can mimic the tissue-tissue interfaces or ADME processes in the body [98], reproduce the drug pharmacokinetic profiles in the body [99], and help to make an early phase decision in drug development by providing efficacy and toxicity results of drugs on an organ level [100]. The microfluidic platforms mainly facilitate pharmacokinetic and pharmacodynamics data extraction at the organism level. It is now expected that more complex devices in the future will help deliver valuable large-scale data sets for the drug discovery processes. Cells derived from patients could even help lay the foundation for personalized drug development and provide the opportunity to optimize drug concentrations for either individual patients or different groups of patients. Additionally, "Lab-on-a-chip" devices are now increasing affecting the drug discovery process [101]. In the preclinical phase, *in vitro* and *in vivo* models based on the lab-on-a-chip technique are being used for the pheno-typical screenings, which allow for higher reliability and better control than traditional *in vitro* assays, to better model the human system. In the future, such devices may deliver valuable information about the underlying mechanisms of the blood-tissue interface relating to the bioavailability of new drugs.

EVIDENCE OF ANTIDIABETIC DRUG DISCOVERY FROM NATURAL PRODUCTS

Natural products have a long history of being used either directly or developed into antidiabetic drugs. Ongoing phases of clinical trials on natural product-derived active components identify natural products as a potential origin for new drug discovery. The discovery of Metformin signifies the most successful finding of an antidiabetic drug from natural products. Guanide, which is the parent compound, was first purified from the plant Goat's Rue [84]. Furthermore, chemical modification of guanide produced biguanide/metformin to improve its efficacy and to reduce toxicity. Phlorizin, a chemical isolated from apple tree bark, was used to develop drugs as sodium-glucose co-transporter (SGLT) inhibitors. Among the most advanced SGLT2 inhibitors (Phlorizin analogs), Canagliflozin, Dapagliflozin and Empagliflozin are approved in the USA, the European Union (EU), Japan and other countries. Three other analogs (Ipragliflozin, Luseogliflozin, and Tofogliflozin) have been approved for usage only in Japan. The Ertugliflozin analog is currently under phase III trials, and a Sotagliflozin analog has just completed a phase II trial [102]. Ruboxistaurin (LY 333531), a protein kinase C (PKC) inhibitor, is currently under an additional phase III investigation by Eli Lilly and Company for treating microvascular complications of diabetes, and Trodusquemine, which is isolated from dogfish (*Squalus acanthias*), is used for T2DM treatment [80]. Exenatide (Byetta®) which act as a mimetics of incretins hormones, isolated from *Heloderma suspectum,* are used as adjunctive therapy for T2DM [80]. Exenatide is the synthetic form of naturally occurring exendin-4 which acts by binding with GLP-1 receptors on β-cells. This interaction enhances glucose-mediated insulin secretion and suppresses glucagon secretion. According to a systematic review and meta-analysis, exenatide positively affects blood glucose levels and additionally influences blood pressure and lipid profiles of diabetic patients [103]. Formulation of resveratrol named as "Sirtris" (SRT-501) is currently being developed which targets SIRT1 enzyme that deacetylates proteins involved in cellular regulation and acts by increasing mitochondrial activity. This formulation is considered to be significant against diabetes and obesity. A successful phase IIa trial of "Sirtris" has already been completed in which it was found to be safe and tolerable with 1.25 or 2.5 g of SRT501 oral doses administered twice daily for 28 days in T2DM [104]. Recently, a systematic review

assessing only the randomized controlled clinical trials reported that resveratrol could be a potential candidate for pharmacological management of T2DM as an adjunctive therapy [105].

CONCLUSION AND FUTURE DIRECTION

Antidiabetic drug discovery from natural products is assumed to be free from side-effects as compared to conventional drugs. As numerous natural products have displayed antidiabetic potential both in animal studies and clinical trials, they can be targeted as the single most dynamic source of lead identification for new antidiabetic drug discovery. The synergistic capability of natural products can also be helpful as the combination therapy for managing T2DM.

More studies are warranted to identify the active compounds from natural products as well as to evaluate the active compounds' activity and efficacy *in vitro* and *in vivo* studies. Moreover, the synergistic interaction of natural products/lead compounds with antidiabetic drugs requires attention because a combination therapy may be effective for reducing the dose and adverse effects of antidiabetic drugs in T2DM treatment. However, assessment of the interaction between drugs and natural products is vital but difficult while performing combination therapy. Some important issues such as stability, selectivity, bioavailability, dosing strategy, optimal dose amount and any adverse effects must be carefully addressed and verified with animal models for natural products during their interaction with drugs. A perfect pharmacokinetic and pharmacodynamics match of these combinations can lead to maximum benefits for T2DM management.

LIST OF ABBREVIATIONS

C-3-R	=	Cyandin-3-rutinoside
DPP-4	=	Dipeptidyl peptidase-4
GLUT4	=	Glucose transporter 4
IR	=	Insulin receptor
PPAR-γ	=	Peroxisome proliferator-activated receptor γ
ROS	=	Reactive oxygen species
STZ	=	Streptozotocin
SU	=	Sulfonylureas
T2DM	=	Type 2 diabetes mellitus

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

We would like to acknowledge Universiti Sains Malaysia (USM) for the Research University (RU) grant - 1001/PPSP/812115. We would also like to acknowledge USM Global Fellowship (2014/2015) and USM Vice-Chancellor Award (2015/2016) awarded to Fahmida Alam and Md. Asiful Islam, respectively, to pursue their PhD degrees.

REFERENCES

[1] Guariguata, L.; Whiting, D.; Hambleton, I.; Beagley, J.; Linnenkamp, U.; Shaw, J. Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Res. Clin. Pract.,* **2014**, *103*(2), 137-149.

[2] Nolan, C.J.; Damm, P.; Prentki, M. Type 2 diabetes across generations: from pathophysiology to prevention and management. *The Lancet,* **2011**, *378*(9786), 169-181.

[3] Inzucchi, S.E.; Bergenstal, R.M.; Buse, J.B.; Diamant, M.; Ferrannini, E.; Nauck, M.; Peters, A.L.; Tsapas, A.; Wender, R.; Matthews, D.R. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care,* **2015**, *38*(1), 140-149.

[4] Hex, N.; Bartlett, C.; Wright, D.; Taylor, M.; Varley, D. Estimating the current and future costs of Type 1 and Type 2 diabetes in the UK, including direct health costs and indirect societal and productivity costs. *Diabet. Med.,* **2012**, *29*(7), 855-862.

[5] Grimes, R.; Bennett, K.; Canavan, R.; Tilson, L.; Henman, M. The impact of initial antidiabetic agent and use of monitoring agents on prescription costs in newly treated type 2 diabetes: a retrospective cohort analysis. *Diabetes Res. Clin. Pract.,* **2016**, *113,* 152-159.

[6] Association, A.D. Economic costs of diabetes in the US in 2012. *Diabetes Care,* **2013**, *36*(4), 1033-1046.

[7] Ng, C.S.; Toh, M.P.H.S.; Ko, Y.; Lee, J.Y.C. Direct medical cost of type 2 diabetes in Singapore. *PLoS ONE,* **2015**, *10*(3), e0122795.

[8] Alam, F.; Islam, M.A.; Khalil, M.I.; Gan, S.H. Metabolic control of type 2 diabetes by targeting the GLUT4 glucose transporter: intervention approaches. *Curr. Pharm. Des.,* **2016**, *22*(20), 3034-3049.

[9] Carter, P.; Gray, L.J.; Troughton, J.; Khunti, K.; Davies, M.J. Fruit and vegetable intake and incidence of type 2 diabetes mellitus: systematic review and meta-analysis. *BMJ,* **2010**, *341*(c4229.

[10] Prabhakar, P.; Kumar, A.; Doble, M. Combination therapy: a new strategy to manage diabetes and its complications. *Phytomedicine,* **2014**, *21*(2), 123-130.

[11] Lahlou, M. Screening of natural products for drug discovery. *Expert. Opin. Drug Discov.,* **2007**, *2*(5), 697-705.

[12] Ye, J.M.; Stanley, M. Strategies for the discovery and development of anti-diabetic drugs from the natural products of traditional medicines. *J. Pharm. Pharm. Sci.,* **2013**, *16*(2), 207-216.

[13] Zakowski, J.J.; Bruns, D.E. Biochemistry of human alpha amylase isoenzymes. *CRC Crit. Rev. Clin. Lab. Sci.,* **1985**, *21*(4), 283-322.
[14] Chiba, S. Molecular mechanism in α-glucosidase and glucoamylase. *Biosci. Biotechnol. Biochem.,* **1997**, *61*(8), 1233-1239.
[15] Tundis, R.; Loizzo, M.; 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*(4), 315-331.
[16] Huang, S.; Czech, M.P. The GLUT4 glucose transporter. *Cell Metab.,* **2007**, *5*(4), 237-252.
[17] Thorens, B.; Mueckler, M. Glucose transporters in the 21st Century. *Am. J. Physiol. Endocrinol. Metab.,* **2010**, *298*(2), E141-E145.
[18] Watson, R.T.; Kanzaki, M.; Pessin, J.E. Regulated membrane trafficking of the insulin-responsive glucose transporter 4 in adipocytes. *Endocr. Rev.,* **2004**, *25*(2), 177-204.
[19] Scrutton, M.C.; Utter, M.F. The regulation of glycolysis and gluconeogenesis in animal tissues. *Annu. Rev. Biochem.,* **1968**, *37*(1), 249-302.
[20] Cernea, S.; Dobreanu, M. Diabetes and beta cell function: from mechanisms to evaluation and clinical implications. *Biochemia medica,* **2013**, *23*(3), 266-280.
[21] Solayman, M.; Ali, Y.; Alam, F.; Islam, M.A.; Alam, N.; Khalil, M.I.; Gan, S.H. Polyphenols: potential future arsenals in the treatment of diabetes. *Curr. Pharm. Des.,* **2016**, *22*(5), 549-565.
[22] Betteridge, D.J. What is oxidative stress? *Metabolism.,* **2000**, *49*(2), 3-8.
[23] Matough, F.A.; Budin, S.B.; Hamid, Z.A.; Alwahaibi, N.; Mohamed, J. The role of oxidative stress and antioxidants in diabetic complications. *Sultan Qaboos Univ. Med. J.,* **2012**, *12*(1), 5.
[24] Asmat, U.; Abad, K.; Ismail, K. Diabetes mellitus and oxidative stress—a concise review. *Saudi Pharm. J.,* **2015**.
[25] Phung, O.; Sood, N.; Sill, B.; Coleman, C. Oral anti-diabetic drugs for the prevention of Type 2 diabetes. *Diabet. Med.,* **2011**, *28*(8), 948-964.
[26] Cicero, A.; Tartagni, E.; Ertek, S. Metformin and its clinical use: new insights for an old drug in clinical practice. *Arch. Med. Sci.,* **2012**, *8*(5), 907-917.
[27] Sola, D.; Rossi, L.; Schianca, G.P.C.; Maffioli, P.; Bigliocca, M.; Mella, R.; Corlianò, F.; Fra, G.P.; Bartoli, E.; Derosa, G. Sulfonylureas and their use in clinical practice. *Arch. Med. Sci.,* **2015**, *11*(4), 840.
[28] Derosa, G.; Maffioli, P. Thiazolidinediones plus metformin association on body weight in patients with type 2 diabetes. *Diabetes Res. Clin. Pract.,* **2011**, *91*(3), 265-270.
[29] Derosa, G.; Maffioli, P. α-Glucosidase inhibitors and their use in clinical practice. *Arch. Med. Sci.,* **2012**, *8*(5), 899-906.
[30] Derosa, G.; Maffioli, P. Dipeptidyl peptidase-4 inhibitors: 3 years of experience. *Diabetes Technol. Ther.,* **2012**, *14*(4), 350-364.
[31] Derosa, G.; Maffioli, P. GLP-1 agonists exenatide and liraglutide: a review about their safety and efficacy. *Curr. Clin. Pharmacol.,* **2012**, *7*(3), 214-228.
[32] Bressler, R.; Johnson, D.G. Pharmacological regulation of blood glucose levels in non--insulin-department diabetes mellitus. *Arch. Intern. Med.,* **1997**, *157*(8), 836.
[33] Acharya, K.G.; Shah, K.N.; Solanki, N.D.; Rana, D.A. Evaluation of antidiabetic prescriptions, cost and adherence to treatment guidelines: A prospective, cross-sectional study at a tertiary care teaching hospital. *J. Basic Clin. Pharm.,* **2013**, *4*(4), 82.
[34] Signorovitch, J.E.; Macaulay, D.; Diener, M.; Yan, Y.; Wu, E.Q.; Gruenberger, J.B.; Frier, B.M. Hypoglycaemia and accident risk in people with type 2 diabetes mellitus treated with non-insulin antidiabetes drugs. *Diabetes Obes. Metab.,* **2013**, *15*(4), 335-341.
[35] Hsu, P.F.; Sung, S.H.; Cheng, H.M.; Yeh, J.S.; Liu, W.L.; Chan, W.L.; Chen, C.H.; Chou, P.; Chuang, S.Y. Association of clinical symptomatic hypoglycemia with cardiovascular events and total mortality in type 2 diabetes a nationwide population-based study. *Diabetes Care,* **2013**, *36*(4), 894-900.
[36] Punthakee, Z.; Miller, M.E.; Launer, L.J.; Williamson, J.D.; Lazar, R.M.; Cukierman-Yaffee, T.; Seaquist, E.R.; Ismail-Beigi, F.; Sullivan, M.D.; Lovato, L.C. Poor Cognitive Function and Risk of Severe Hypoglycemia in Type 2 Diabetes Post hoc epidemiologic analysis of the ACCORD trial. *Diabetes Care,* **2012**, *35*(4), 787-793.
[37] Yanai, H.; Adachi, H.; Katsuyama, H.; Moriyama, S.; Hamasaki, H.; Sako, A. Causative anti-diabetic drugs and the underlying clinical factors for hypoglycemia in patients with diabetes. *World J. Diabetes,* **2015**, *6*(1), 30.
[38] Badole, S.L.; Bodhankar, S.L. Effect of concomitant administration of aqueous extract of *Pleurotus pulmonarius* and metformin in diabetic mice. *J. Complementary Integr. Med.,* **2008**, *5*(1).
[39] Atal, S.; Atal, S.; Vyas, S.; Phadnis, P. Bio-enhancing effect of Piperine with Metformin on lowering blood glucose level in Alloxan induced diabetic mice. *Pharmacogn. Res.,* **2016**, *8*(1), 56.
[40] Reddy, R.; Sunitha, P.; Srikanth, P. Beneficial effect of ethanolic extract of bael fruit in combination with metformin hcl in normal rabbits. *Int. J. Res. Pharm. Chem.,* **2011**, *1*(3), 528-534.
[41] Tripathi, P.; Gupta, P.P.; Lal, V.K. Effect of Co-administration of *Allium sativum* extract and metformin on blood glucose of Streptozotocin induced diabetic rats. *J. Intercult. Ethnopharmacol.,* **2013**, *2*(2), 81-84.
[42] Poonam, T.; Prakash, P.; Kumar, V. Interaction of *Momordica charantia* with metformin in diabetic rats. *Am. J. Pharmacol. Toxicol.,* **2013**, *8*(3), 102-106.
[43] Wang, X.; Chen, Y.; Abdelkader, D.; Hassan, W.; Sun, H.; Liu, J. Combination therapy with oleanolic acid and metformin as a synergistic treatment for diabetes. *J. Diabetes Res.,* **2015**, *2015*, 1-12.
[44] Elango, H.; Ponnusankar, S.; Sundaram, S. Assessment of pharmacodynamic and pharmacokinetic interaction of aqueous extract of *Cassia auriculata* L. and metformin in rats. *Pharmacogn. Mag.,* **2015**, *11*(44), 423.
[45] Idakwoji, P.A.; Salawu, O.A.; Maiha, B.B.; Obidike, I.; Tijani, A.Y. Co-administeration of ethanolic leaf extract of *moringa oleifera* and metformin improves glucose, lipid and protein profiles of diabetic wistar rats. *Biokemistri,* **2015**, *27*(3), 129-138.
[46] Bairy, K.; Adarsh, K.; Shalini, A. Effect of concomitant administration of aqueous extract of leaves of *trichosanthes dioica* and metformin in streptozotocin induced diabetic rats. *Int. J. Adv. Res.,* **2015**, *3*(3), 1034-1038.
[47] Eissa, L.A.; Abdel-Rahman, N.; Eraky, S.M. Effects of omega-3 fatty acids and pioglitazone combination on insulin resistance through fibroblast growth factor 21 in type 2 diabetes mellitus. *Egypt. J. Basic Appl. Sci.,* **2015**, *2*(2), 75-86.
[48] Nankar, R.P.; Doble, M. Ellagic acid potentiates insulin sensitising activity of pioglitazone in L6 myotubes. *J. Funct. Foods,* **2015**, *15*, 1-10.
[49] Prasad Neerati, R.K.M.; Kanwar, J.R. Influence of curcumin on pioglitazone metabolism and Pk/Pd: diabetes mellitus. *J. Diabetes Metab.,* **2013**, *2013*, 1-7.

[50] Gayasuddin, M.; Shakil, S.; Kavimani, S. Effect of ethanolic extract of *Piper cubeba* Linn. fruits on activity of pioglitazone. *Int. J. Pharm. Indust. Res.,* **2011**, *1*, 312-314.

[51] Grover, N.; Bafna, P. Protective effect of coadministration of *Cassia auriculata* and pioglitazone in diabetic rats. *Eur. J. Exp. Biol.,* **2013**, *3*(2), 231-241.

[52] Grover, N.; Bafna, P. Effects of Coadministration of *Cassia auriculata* and Pioglitazone in Alloxan Treated Diabetic Rats. *Int. J. Adv. Pharm. Res.,* **2011**, *2*, 621-629.

[53] Gao, J.; Xu, P.; Wang, Y.; Wang, Y.; Hochstetter, D. Combined effects of green tea extracts, green tea polyphenols or epigallocatechin gallate with acarbose on inhibition against α-amylase and α-glucosidase *in vitro*. *Molecules,* **2013**, *18*(9), 11614-11623.

[54] Boath, A.S.; Stewart, D.; McDougall, G.J. Berry components inhibit α-glucosidase *in vitro*: Synergies between acarbose and polyphenols from black currant and rowanberry. *Food. Chem.,* **2012**, *135*(3), 929-936.

[55] Badole, S.L.; Bodhankar, S.L. Interaction of aqueous extract of *Pleurotus pulmonarius* (Fr.) Quel-champ. with acarbose in alloxan induced diabetic mice. *Interaction,* **2007**, *5*(3), 157-166.

[56] Adisakwattana, S.; Charoenlertkul, P.; Yibchok-anun, S. α-Glucosidase inhibitory activity of cyanidin-3-galactoside and synergistic effect with acarbose. *J. Enzyme Inhib. Med. Chem.,* **2009**, *24*(1), 65-69.

[57] Akkarachiyasit, S.; Yibchok-Anun, S.; Wacharasindhu, S.; Adisakwattana, S. *In vitro* inhibitory effects of cyandin-3-rutinoside on pancreatic α-amylase and its combined effect with acarbose. *Molecules,* **2011**, *16*(3), 2075-2083.

[58] Adisakwattana, S.; Yibchok-Anun, S.; Charoenlertkul, P.; Wongsasiripat, N. Cyanidin-3-rutinoside alleviates postprandial hyperglycemia and its synergism with acarbose by inhibition of intestinal. ALPHA.-glucosidase. *J. Clin. Biochem. Nutr.,* **2011**, *49*(1), 36-41.

[59] Akkarachiyasit, S.; Charoenlertkul, P.; Yibchok-anun, S.; Adisakwattana, S. Inhibitory activities of cyanidin and its glycosides and synergistic effect with acarbose against intestinal α-glucosidase and pancreatic α-amylase. *Int. J. Mol. Sci.,* **2010**, *11*(9), 3387-3396.

[60] Devi, P.S.; Reddy, A.G.; Rao, G.; Kumar, C.S.; Boobalan, G. Pharmacokinetic interaction of curcumin and glibenclamide in diabetic rats. *Vet. World,* **2015**, *8*(4), 508-511.

[61] Poonam, T.; Prakash, G.P.; Kumar, L.V. Influence of *Allium sativum* extract on the hypoglycemic activity of glibenclamide: an approach to possible herb-drug interaction. *Drug Metabol. Drug Interact.,* **2013**, *28*(4), 225-230.

[62] Sankar, D.; Ali, A.; Sambandam, G.; Rao, R. Sesame oil exhibits synergistic effect with anti-diabetic medication in patients with type 2 diabetes mellitus. *Clin. Nutr.,* **2011**, *30*(3), 351-358.

[63] Lal, V.; Gupta, P.; Tripathi, P.; Pandey, A. Interaction of *Momordica charantia* fruit juice with glibenclamide in streptozotocin induced diabetic rats. *Pharmacol. Online,* **2011**, *3*(853-857.

[64] Heroor, S.; Beknal, A.; Mahurkar, N. Ficus bark extract enhances the antihyperglycemic activity of glibenclamide in rats: a herb-drug interaction study. *Am. J. Phytomed. Clin. Ther.,* **2014**, *2*(3), 395-402.

[65] Heroor, S.; Beknal, A.; Mahurkar, N. Effect of Pongamia Bark Extract on antihyperglycemic effect of glibenclamide for possible herb-drug interaction. *Ind. J. Pharm. Edu. Res.,* **2015**, *49*(1), 76-81.

[66] Khayatnouri, M.; Bahari, K.; Safarmashaei, S. Study of the effect of gliclazide and garlic extract on blood sugar level in STZ-induced diabetic male mice. *Adv. Environ. Biol.,* **2011**, 1751-1756.

[67] Khayatnouri, M.; Nikmanesh, M.; Safarmashaei, S. Study of the effect of gliclazide and carrot juice on blood sugar level in STZ-induced diabetic male mice. *Adv. Environ. Biol.,* **2011**, *5*(7), 1742-1746.

[68] Mastan, S.; Latha, T.B.; Latha, T.S.; Srikanth, A.; Chaitanya, G.; Kumar, K.E. Influence of methanolic extract of *Syzygium cumini* seeds on the activity of gliclazide in normal and alloxan-induced diabetic rats. *Pharmacology Online,* **2009**, *3*, 845-850.

[69] Mouid, M.G. Effect of ethanolic extract of aerial parts of *Andrographis paniculata* on the pharmacokinetics of gliclazide in rats. *Asian J. Biomed. Pharm. Sci.,* **2015**, *5*(51), 21.

[70] Raju, M.G.; Satynarayana, K.E. Safety of Gliclazide with the aqueous extract of *Tinospora Cordifolia* on pharmacodynamic activity in normal and alloxan induced diabetic rats. *Indo Am. J. Pharm. Res.,* **2014**, *4*(04), 1910-1916.

[71] Satyanarayana, S.; Eswar Kumar, K.; Cooty, T.; Rajanna, S.; Rajanna, B. Influence of an aqueous extract of *Azadirachta indica* leaf on the pharmacodynamics and pharmacokinetics of gliclazide in rats and rabbits. *J. Herbs, Spices Med. Plants,* **2009**, *15*(1), 16-23.

[72] Satyanarayana, S.; Eswar Kumar, K.; Rajasekhar, J.; Thomas, L.; Rajanna, S.; Rajanna, B. Influence of aqueous extract of fenugreek-seed powder on the pharmacodynamics and pharmacokinetics of gliclazide in rats/rabbits. *Fut. Med.,* **2007**, *4*(4), 457-463.

[73] Dholi, S.K.; Raparla, R. Effect of *Gymnema sylvestre* on the pharmacokinetic and pharmacodynamic of oral hypoglycemic drug-gliclazide in streptozotocin induced diabetic rats. *Annu. Res. Rev. Biol.,* **2014**, *4*(22), 3373.

[74] Raju, M.G.; Satyanarayana, S.; Kumar, E. Safety of gliclazide with the aqueous extract of *Gymnema sylvestre* on pharmacodynamic activity in normal and alloxan induced diabetic rats. *Am. J. Phytomed. Clin. Ther.,* **2014**, *2*(7), 901-909.

[75] Rani, T.S.; Sujatha, S.; Veeresham, C. Pharmacokinetic and pharmacodynamic interaction of curcumin with glimepiride in normal and diabetic rats. *Pharmacognosy Communications,* **2012**, *2*(3), 14-21.

[76] Veeresham, C.; Sujatha, S.; Rani, T.S. Effect of piperine on the pharmacokinetics and pharmacodynamics of glimepiride in normal and streptozotocin-induced diabetic rats. *Nat. Prod. Commun.,* **2012**, *7*(10), 1283-1286.

[77] Mittal, P.; Juyal, V. Drug-dietary interaction potential of garlic on glimepiride treated type 2 diabetic Wistar rats. *J.Diabetol.,* **2012**, *3*, 2, 1-8.

[78] Ahmad, M.F.; Keservani, R.K.; Babu, D.M. Interaction study between *Ocimum sanctum* and Glimepiride (sulfonylurea derivative) in diabetic rats. *J. Chin. Pharm. Sci.,* **2015**, *24*(3), 156-163.

[79] Balunas, M.J.; Kinghorn, A.D. Drug discovery from medicinal plants. *Life Sci.,* **2005**, *78*(5), 431-441.

[80] Mishra, B.B.; Tiwari, V.K. Natural products: an evolving role in future drug discovery. *Eur. J. Med. Chem.,* **2011**, *46*(10), 4769-4807.

[81] Butler, M.S. The role of natural product chemistry in drug discovery. *J. Nat. Prod.,* **2004**, *67*(12), 2141-2153.

[82] Reichert, J.M. Trends in development and approval times for new therapeutics in the United States. *Nat. Rev. Drug Discovery,* **2003**, *2*(9), 695-702.

[83] Dickson, M.; Gagnon, J.P. Key factors in the rising cost of new drug discovery and development. *Nat. Rev. Drug Discov.,* **2004**, *3*(5), 417-429.

[84] Koehn, F.E.; Carter, G.T. The evolving role of natural products in drug discovery. *Nat. Rev. Drug Discov.,* **2005**, *4*(3), 206-220.

[85] Do, Q.T.; Bernard, P. Pharmacognosy and reverse pharmacognosy: a new concept for accelerating natural drug discovery. *IDrugs,* **2004**, *7*(11), 1017-1027.

[86] Soejarto, D.D.; Gyllenhaal, C.; Fong, H.; Xuan, L.T.; Hiep, N.T.; Hung, N.; Bich, T.Q.; Southavong, B.; Sydara, K.; Pezzuto, J.M. A model of benefit-sharing arrangement in natural products drug discovery and development. *J. Nat. Prod.,* **2004**, *67*(2), 294-299.

[87] Walters, W.P.; Namchuk, M. Designing screens: how to make your hits a hit. *Nat. Rev. Drug Discovery,* **2003**, *2*(4), 259-266.

[88] Eldridge, G.R.; Vervoort, H.C.; Lee, C.M.; Cremin, P.A.; Williams, C.T.; Hart, S.M.; Goering, M.G.; O'Neil-Johnso, M.; Zeng, L. High-throughput method for the production and analysis of large natural product libraries for drug discovery. *Anal. Chem.,* **2002**, *74*(16), 3963-3971.

[89] Pellecchia, M.; Sem, D.S.; Wüthrich, K. NMR in drug discovery. *Nat. Rev. Drug Discovery,* **2002**, *1*(3), 211-219.

[90] Blundell, T.L.; Jhoti, H.; Abell, C. High-throughput crystallography for lead discovery in drug design. *Nat. Rev. Drug Discovery,* **2002**, *1*(1), 45-54.

[91] Ley, S.V.; Baxendale, I.R. New tools and concepts for modern organic synthesis. *Nat. Rev. Drug Discovery,* **2002**, *1*(8), 573-586.

[92] Lombardino, J.G.; Lowe, J.A. The role of the medicinal chemist in drug discovery—then and now. *Nat. Rev. Drug Discovery,* **2004**, *3*(10), 853-862.

[93] Islam, M.A.; Alam, F.; Khalil, M.I.; Sasongko, T.H.; Gan, S.H. Natural products towards the discovery of potential future antithrombotic drugs. *Curr. Pharm. Des.,* **2016**, *22*(20), 2926-2946.

[94] Tan, D.S. Current progress in natural product-like libraries for discovery screening. *Comb. Chem. High Throughput Screen.,* **2004**, *7*(7), 631-643.

[95] Piggott, A.M.; Karuso, P. Quality, not quantity: the role of natural products and chemical proteomics in modern drug discovery. *Comb. Chem. High Throughput Screen.,* **2004**, *7*(7), 607-630.

[96] van Midwoud, P.M.; Verpoorte, E.; Groothuis, G.M. Microfluidic devices for *in vitro* studies on liver drug metabolism and toxicity. *Integr. Biol.,* **2011**, *3*(5), 509-521.

[97] van Midwoud, P.M.; Merema, M.T.; Verpoorte, E.; Groothuis, G.M. A microfluidic approach for *in vitro* assessment of interorgan interactions in drug metabolism using intestinal and liver slices. *Lab. Chip,* **2010**, *10*(20), 2778-2786.

[98] Esch, M.; King, T.; Shuler, M. The role of body-on-a-chip devices in drug and toxicity studies. *Annu. Rev. Biomed. Eng.,* **2011**, *13*, 55-72.

[99] Sung, J.H.; Shuler, M.L. A micro cell culture analog (μCCA) with 3-D hydrogel culture of multiple cell lines to assess metabolism-dependent cytotoxicity of anti-cancer drugs. *Lab. Chip,* **2009**, *9*(10), 1385-1394.

[100] Huh, D.; Matthews, B.D.; Mammoto, A.; Montoya-Zavala, M.; Hsin, H.Y.; Ingber, D.E. Reconstituting organ-level lung functions on a chip. *Science,* **2010**, *328*(5986), 1662-1668.

[101] Neuži, P.; Giselbrecht, S.; Länge, K.; Huang, T.J.; Manz, A. Revisiting lab-on-a-chip technology for drug discovery. *Nat. Rev. Drug Discov.,* **2012**, *11*(8), 620-632.

[102] Mudaliar, S.; Polidori, D.; Zambrowicz, B.; Henry, R.R. Sodium–glucose cotransporter inhibitors: effects on renal and intestinal glucose transport from bench to bedside. *Diabetes Care,* **2015**, *38*(12), 2344-2353.

[103] Nikfar, S.; Abdollahi, M.; Salari, P. The efficacy and tolerability of exenatide in comparison to placebo; a systematic review and meta-analysis of randomized clinical trials. *J. Pharm. Pharm. Sci.,* **2011**, *15*(1), 1-30.

[104] Lambert, D.M.; Fowler, C.J. The endocannabinoid system: drug targets, lead compounds, and potential therapeutic applications. *J. Med. Chem.,* **2005**, *48*(16), 5059-5087.

[105] Hausenblas, H.A.; Schoulda, J.A.; Smoliga, J.M. Resveratrol treatment as an adjunct to pharmacological management in type 2 diabetes mellitus—systematic review and meta-analysis. *Mol. Nutr. Food Res.,* **2015**, *59*(1), 147-159.

[106] Lavelli, V.; Harsha, P.S.; Ferranti, P.; Scarafoni, A.; Iametti, S. Grape skin phenolics as inhibitors of mammalian α-glucosidase and α-amylase–effect of food matrix and processing on efficacy. *Food Funct.,* **2016**, *7*(3), 1655-1663.

[107] Zhou, F.; Furuhashi, K.; Son, M.J.; Toyozaki, M.; Yoshizawa, F.; Miura, Y.; Yagasaki, K. Antidiabetic effect of enterolactone in cultured muscle cells and in type 2 diabetic model db/db mice. *Cytotechnology,* **2016**, 1-10. [Epub ahead of print]

[108] Johnson, M.H.; de Mejia, E.G. Phenolic compounds from fermented berry beverages modulated gene and protein expression to increase insulin secretion from pancreatic β-cells *in vitro*. *J. Agric. Food Chem.,* **2016**. [Epub ahead of print].

[109] Gao, M.; Zhao, Z.; Lv, P.; Li, Y.; Gao, J.; Zhang, M.; Zhao, B. Quantitative combination of natural anti-oxidants prevents metabolic syndrome by reducing oxidative stress. *Redox biology,* **2015**, *6*, 206-217.

[110] Cui, J.; Gu, X.; Wang, F.; Ouyang, J.; Wang, J. Purification and structural characterization of an α-glucosidase inhibitory polysaccharide from apricot (*Armeniaca sibirica* L. Lam.) pulp. *Carbohydr. Polym.,* **2015**, *121*, 309-314.

[111] Cho, S.J.; Jung, U.J.; Kim, H.J.; Ryu, R.; Ryoo, J.Y.; Moon, B.S.; Choi, M.S. Effects of the combined extracts of grape pomace and omija fruit on hyperglycemia and adiposity in type 2 diabetic mice. *Prev. Nutr. Food Sci.,* **2015**, *20*(2), 94.

[112] Yin, W.; Li, B.; Li, X.; Yu, F.; Cai, Q.; Zhang, Z.; Cheng, M.; Gao, H. Anti-inflammatory effects of grape seed procyanidin B2 on a diabetic pancreas. *Food Funct.,* **2015**, *6*(9), 3065-3071.

[113] Cui, J.; Gu, X.; Zhang, Q.; Ou, Y.; Wang, J. Production and anti-diabetic activity of soluble dietary fiber from apricot pulp by Trichoderma viride fermentation. *Food Funct.,* **2015**, *6*(5), 1635-1642.

[114] Patel, I.; Padse, O.; Ingole, Y. Comparative Analysis of Antioxidant domestica), Banana (Musa Paradisiaca) & Kiwi (Actinidia deliciosa). In: IJRAT, *National Conference ACGT*, 13-14 February **2015**; Vol. *2015*, pp. 28-31.

[115] Saravanan, S.; Parimelazhagan, T. *In vitro* antioxidant, antimicrobial and anti-diabetic properties of polyphenols of *Passiflora ligularis* Juss. fruit pulp. *Food Sci. Hum. Wellness,* **2014**, *3*(2), 56-64.

[116] de la Garza, A.L.; Etxeberria, U.; Palacios-Ortega, S.; Haslberger, A.G.; Aumueller, E.; Milagro, F.I.; Martínez, J.A. Modulation of hyperglycemia and TNFα-mediated inflammation by helichrysum and grapefruit extracts in diabetic db/db mice. *Food Funct.,* **2014**, *5*(9), 2120-2128.

[117] Schulze, C.; Bangert, A.; Kottra, G.; Geillinger, K.E.; Schwanck, B.; Vollert, H.; Blaschek, W.; Daniel, H. Inhibition of the intestinal sodium-coupled glucose transporter 1 (SGLT1) by extracts and polyphenols from apple reduces postprandial blood glucose levels in mice and humans. *Mol. Nutr. Food Res.,* **2014**, *58*(9), 1795-1808.

[118] Oboh, G.; Isaac, A.T.; Akinyemi, A.J.; Ajani, R.A. Inhibition of key enzymes linked to type 2 diabetes and sodium nitroprusside induced lipid peroxidation in rats' pancreas by phenolic extracts of avocado pear leaves and fruit. *Int. J. Biomed. Sci.,* **2014**, *10*(3), 208.

[119] Cedó, L.; Castell-Auví, A.; Pallarès, V.; Blay, M.; Ardévol, A.; Arola, L.; Pinent, M. Grape seed procyanidin extract

modulates proliferation and apoptosis of pancreatic beta-cells. *Food. Chem.,* **2013**, *138*(1), 524-530.

[120] Shafi, S.; Tabassum, N. Anti-diabetic and Hypolipidemic activities of ethanolic extract of *Eriobotrya Japonica* fruits in Alloxan induced diabetic rats. *Int. J. Pharm., Chem. Biol. Sci.,* **2013**, *3*(2), 398-405.

[121] Rojo, L.E.; Ribnicky, D.; Logendra, S.; Poulev, A.; Rojas-Silva, P.; Kuhn, P.; Dorn, R.; Grace, M.H.; Lila, M.A.; Raskin, I. *In vitro* and *in vivo* anti-diabetic effects of anthocyanins from Maqui Berry (*Aristotelia chilensis*). *Food. chem.,* **2012**, *131*(2), 387-396.

[122] González-Abuín, N.; Martínez-Micaelo, N.; Blay, M.; Pujadas, G.; Garcia-Vallvé, S.; Pinent, M.; Ardévol, A. Grape seed-derived procyanidins decrease dipeptidyl-peptidase 4 activity and expression. *J. Agric. Food Chem.,* **2012**, *60*(36), 9055-9061.

[123] Shen, S.C.; Chang, W.C.; Chang, C.L. Fraction from wax apple [*Syzygium samarangense* (Blume) Merrill and Perry] fruit extract ameliorates insulin resistance via modulating insulin signaling and inflammation pathway in tumor necrosis factor α-treated FL83B mouse hepatocytes. *Int. J. Mol. Sci.,* **2012**, *13*(7), 8562-8577.

[124] Kannan, V.R.; Rajasekar, G.S.; Rajesh, P.; Balasubramanian, V.; Ramesh, N.; Solomon, E.K.; Nivas, D.; Chandru, S. Anti-diabetic activity on ethanolic extracts of fruits of *Terminalia chebula* Retz. Alloxan induced diabetic rats. *Am. J. Drug Discov. Devel.,* **2012**, *2*, 135-142.

[125] Park, J.H.; Kim, R.Y.; Park, E. Antidiabetic activity of fruits and vegetables commonly consumed in Korea: Inhibitory potential against α-glucosidase and insulin-like action *in vitro*. *Food Sci. Biotechnol.,* **2012**, *21*(4), 1187-1193.

[126] Sharma, U.; Kumar, A. Anti-diabetic effect of *Rubus ellipticus* fruits extracts in alloxan-induced diabetic rats. *J. Diabetol.,* **2011**, *2*(4).

[127] Johnson, M.H.; Lucius, A.; Meyer, T.; Gonzalez de Mejia, E. Cultivar evaluation and effect of fermentation on antioxidant capacity and *in vitro* inhibition of α-amylase and α-glucosidase by highbush blueberry (Vaccinium corombosum). *J. Agric. Food Chem.,* **2011**, *59*(16), 8923-8930.

[128] De Souza Schmidt Goncalves, A.E.; Lajolo, F.M.; Genovese, M.I. Chemical composition and antioxidant/antidiabetic potential of Brazilian native fruits and commercial frozen pulps. *J. Agric. Food Chem.,* **2010**, *58*(8), 4666-4674.

[129] Sharma, B.; Salunke, R.; Balomajumder, C.; Daniel, S.; Roy, P. Anti-diabetic potential of alkaloid rich fraction from *Capparis decidua* on diabetic mice. *J. Ethnopharmacol.,* **2010**, *127*(2), 457-462.

[130] Azadbakhta, M.; Safapour, S.; Ahmadi, A.; Ghasemi, M.; Shokrzadeh, M. Anti-diabetic effects of aqueous fruits extract of *Diospyros lotus* L. on streptozotocin-induced diabetic rats and the possible morphologic changes in the liver, kidney and heart. *J. Pharmacog. Phytother.,* **2010**, *2*, 10-16.

[131] Cheplick, S.; Kwon, Y.I.; Bhowmik, P.; Shetty, K. Phenolic-linked variation in strawberry cultivars for potential dietary management of hyperglycemia and related complications of hypertension. *Bioresour. Technol.,* **2010**, *101*(1), 404-413.

[132] Seymour, E.; Lewis, S.K.; Urcuyo-Llanes, D.E.; Tanone, I.I.; Kirakosyan, A.; Kaufman, P.B.; Bolling, S.F. Regular tart cherry intake alters abdominal adiposity, adipose gene transcription, and inflammation in obesity-prone rats fed a high fat diet. *J. Med. Food,* **2009**, *12*(5), 935-942.

[133] Kumar, A.; Ilavarasan, R.; Jayachandran, T.; Deecaraman, M.; Aravindan, P.; Padmanabhan, N.; Krishan, M. Anti-diabetic activity of *Syzygium cumini* and its isolated compound against streptozotocin-induced diabetic rats. *J. Med. Plants Res.,* **2008**, *2*(9), 246-249.

[134] Seymour, E.M.; Singer, A.A.; Kirakosyan, A.; Urcuyo-Llanes, D.E.; Kaufman, P.B.; Bolling, S.F. Altered hyperlipidemia, hepatic steatosis, and hepatic peroxisome proliferator-activated receptors in rats with intake of tart cherry. *J. Med. Food,* **2008**, *11*(2), 252-259.

[135] Hwang, I.K.; Kim, D.W.; Park, J.H.; Lim, S.S.; Yoo, K.Y.; Kwon, D.Y.; Kim, D.W.; Moon, W.K.; Won, M.H. Effects of grape seed extract and its ethylacetate/ethanol fraction on blood glucose levels in a model of type 2 diabetes. *Phytother. Res.,* **2009**, *23*(8), 1182-1185.

[136] Martineau, L.C.; Couture, A.; Spoor, D.; Benhaddou-Andaloussi, A.; Harris, C.; Meddah, B.; Leduc, C.; Burt, A.; Vuong, T.; Le, P.M. Anti-diabetic properties of the Canadian lowbush blueberry *Vaccinium angustifolium* Ait. *Phytomedicine,* **2006**, *13*(9), 612-623.

[137] Kumar, G.P.S.; Arulselvan, P.; Kumar, D.S.; Subramanian, S.P. Anti-diabetic activity of fruits of *Terminalia chebula* on streptozotocin induced diabetic rats. *J. Health Sci.,* **2006**, *52*(3), 283-291.

[138] Campbell, J.I.; Mortensen, A.; Mølgaard, P. Tissue lipid lowering-effect of a traditional Nigerian anti-diabetic infusion of Rauwolfia vomitoria foilage and Citrus aurantium fruit. *J. Ethnopharmacol.,* **2006**, *104*(3), 379-386.

[139] Reyes, B.; Bautista, N.; Tanquilut, N.; Anunciado, R.; Leung, A.; Sanchez, G.; Magtoto, R.; Castronuevo, P.; Tsukamura, H.; Maeda, K.I. Anti-diabetic potentials of *Momordica charantia* and *Andrographis paniculata* and their effects on estrous cyclicity of alloxan-induced diabetic rats. *J. Ethnopharmacol.,* **2006**, *105*(1), 196-200.

[140] Utsunomiya, H.; Yamakawa, T.; Kamei, J.; Kadonosono, K.; Tanaka, S.I. Anti-hyperglycemic effects of plum in a rat model of obesity and type 2 diabetes, Wistar fatty rat. *Biomed. Res.,* **2005**, *26*(5), 193-200.

[141] Naito, Y.; Akagiri, S.; Uchiyama, K.; Kokura, S.; Yoshida, N.; Hasegawa, G.; Nakamura, N.; Ichikawa, H.; Toyokuni, S.; Ijichi, T. Reduction of diabetes-induced renal oxidative stress by a cantaloupe melon extract/gliadin biopolymers, oxykine, in mice. *Biofactors,* **2005**, *23*(2), 85-95.

[142] Park, C.J.; Lee, H.A.; Han, J.S. Jicama (*Pachyrhizus erosus*) extract increases insulin sensitivity and regulates hepatic glucose in C57BL/Ksj-db/db mice. *J. Clin. Biochem. Nutr.,* **2016**, *58*(1), 56.

[143] Chen, Y.H.; Lee, C.H.; Hsu, T.H.; Lo, H.C. Submerged-culture mycelia and broth of the maitake medicinal mushroom Grifola frondosa (higher basidiomycetes) alleviate type 2 diabetes-induced alterations in immunocytic function. *Int. J. Med. Mushrooms,* **2015**, *17*(6), 541-556.

[144] Oboh, G.; Ademosun, A.O.; Ademiluyi, A.O.; Omojokun, O.S.; Nwanna, E.E.; Longe, K.O. *In vitro* studies on the antioxidant property and inhibition of α-amylase, α-glucosidase, and angiotensin i-converting enzyme by polyphenol-rich extracts from cocoa (Theobroma cacao) bean. *Patholog. Res. Int.,* **2014**, *2014*, 1-6.

[145] Chang, W.C.; Jia, H.; Aw, W.; Saito, K.; Hasegawa, S.; Kato, H. Beneficial effects of soluble dietary Jerusalem artichoke (*Helianthus tuberosus*) in the prevention of the onset of type 2 diabetes and non-alcoholic fatty liver disease in high-fructose diet-fed rats. *Br. J. Nutr.,* **2014**, *112*(05), 709-717.

[146] Yao, Y.; Cheng, X.; Ren, G. α-Glucosidase inhibitory activity of protein-rich extracts from extruded adzuki bean in diabetic KK-A y mice. *Food Funct.,* **2014**, *5*(5), 966-971.

[147] Su, C.H.; Lu, T.M.; Lai, M.N.; Ng, L.T. Inhibitory potential of *Grifola frondosa* bioactive fractions on α-amylase and α-glucosidase for management of hyperglycemia. *Biotechnol. Appl. Biochem.,* **2013**, *60*(4), 446-452.

[148] Hafizur, R.M.; Kabir, N.; Chishti, S. *Asparagus officinalis* extract controls blood glucose by improving insulin secre-

tion and β-cell function in streptozotocin-induced type 2 diabetic rats. *Br. J. Nutr.,* **2012**, *108*(09), 1586-1595.

[149] Kobayashi, M.; Kawashima, H.; Takemori, K.; Ito, H.; Murai, A.; Masuda, S.; Yamada, K.; Uemura, D.; Horio, F. Ternatin, a cyclic peptide isolated from mushroom, and its derivative suppress hyperglycemia and hepatic fatty acid synthesis in spontaneously diabetic KK-Ay mice. *Biochem. Biophys. Res. Commun.,* **2012**, *427*(2), 299-304.

[150] Kim, S.H.; Jo, S.H.; Kwon, Y.I.; Hwang, J.K. Effects of onion (*Allium cepa* L.) extract administration on intestinal α-glucosidases activities and spikes in postprandial blood glucose levels in SD rats model. *Int. J. Mol. Sci.,* **2011**, *12*(6), 3757-3769.

[151] Thyagarajan-Sahu, A.; Lane, B.; Sliva, D. ReishiMax, mushroom based dietary supplement, inhibits adipocyte differentiation, stimulates glucose uptake and activates AMPK. *BMC Complement. Altern. Med.,* **2011**, *11*(1), 74.

[152] Jung, J.Y.; Lim, Y.; Moon, M.S.; Kim, J.Y.; Kwon, O. Onion peel extracts ameliorate hyperglycemia and insulin resistance in high fat diet/streptozotocin-induced diabetic rats. *Nutr. Metab.,* **2011**, *8*(1), 1-8.

[153] Jeong, S.C.; Jeong, Y.T.; Yang, B.K.; Islam, R.; Koyyalamudi, S.R.; Pang, G.; Cho, K.Y.; Song, C.H. White button mushroom (Agaricus bisporus) lowers blood glucose and cholesterol levels in diabetic and hypercholesterolemic rats. *Nutr. Res.,* **2010**, *30*(1), 49-56.

[154] 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*(14), 1502-1507.

[155] Shin, S.; Lee, S.; Kwon, J.; Moon, S.; Lee, S.; Lee, C.K.; Cho, K.; Ha, N.J.; Kim, K. Cordycepin suppresses expression of diabetes regulating genes by inhibition of lipopolysaccharide-induced inflammation in macrophages. *Immune Netw.,* **2009**, *9*(3), 98-105.

[156] Kwon, Y.I.; Apostolidis, E.; Shetty, K. *In vitro* studies of eggplant (*Solanum melongena*) phenolics as inhibitors of key enzymes relevant for type 2 diabetes and hypertension. *Bioresour. Technol.,* **2008**, *99*(8), 2981-2988.

[157] Hong, L.; Xun, M.; Wutong, W. Anti-diabetic effect of an α-glucan from fruit body of maitake (*Grifola frondosa*) on KK-Ay mice. *J. Pharm. Pharmacol.,* **2007**, *59*(4), 575-582.

[158] Cho, E.J.; Hwang, H.J.; Kim, S.W.; Oh, J.Y.; Baek, Y.M.; Choi, J.W.; Bae, S.H.; Yun, J.W. Hypoglycemic effects of exopolysaccharides produced by mycelial cultures of two different mushrooms *Tremella fuciformis* and *Phellinus baumii* in ob/ob mice. *Appl. Microbiol. Biotechnol.,* **2007**, *75*(6), 1257-1265.

[159] Kuate, D.; Kengne, A.P.N.; Biapa, C.P.N.; Azantsa, B.G.K.; Muda, W.A.M.B.W. Tetrapleura tetraptera spice attenuates high-carbohydrate, high-fat diet-induced obese and type 2 diabetic rats with metabolic syndrome features. *Lipids Health Dis.,* **2015**, *14*(1), 1-13.

[160] Li, Y.; Tran, V.H.; Kota, B.P.; Nammi, S.; Duke, C.C.; Roufogalis, B.D. Preventative Effect of *Zingiber officinale* on Insulin Resistance in a High-Fat High-Carbohydrate Diet-Fed Rat Model and its Mechanism of Action. *Basic Clin. Pharmacol. Toxicol.,* **2014**, *115*(2), 209-215.

[161] Priya Rani, M.; Padmakumari, K.; Sankarikutty, B.; Lijo Cherian, O.; Nisha, V.; Raghu, K. Inhibitory potential of ginger extracts against enzymes linked to type 2 diabetes, inflammation and induced oxidative stress. *Int. J. Food Sci. Nutr.,* **2011**, *62*(2), 106-110.

[162] Lekshmi, P.; Arimboor, R.; Raghu, K.; Menon, A.N. Turmerin, the antioxidant protein from turmeric (*Curcuma longa*) exhibits antihyperglycaemic effects. *Nat. Prod. Res.,* **2012**, *26*(17), 1654-1658.

[163] Lekshmi, P.; Arimboor, R.; Indulekha, P.; Nirmala Menon, A. Turmeric (*Curcuma longa* L.) volatile oil inhibits key enzymes linked to type 2 diabetes. *Int. J. Food Sci. Nutr.,* **2012**, *63*(7), 832-834.

[164] Nishiyama, T.; Mae, T.; Kishida, H.; Tsukagawa, M.; Mimaki, Y.; Kuroda, M.; Sashida, Y.; Takahashi, K.; Kawada, T.; Nakagawa, K. Curcuminoids and sesquiterpenoids in turmeric (*Curcuma longa* L.) suppress an increase in blood glucose level in type 2 diabetic KK-Ay mice. *J. Agric. Food Chem.,* **2005**, *53*(4), 959-963.

[165] Adefegha, S.A.; Oboh, G. Inhibition of key enzymes linked to type 2 diabetes and sodium nitroprusside-induced lipid peroxidation in rat pancreas by water extractable phytochemicals from some tropical spices. *Pharm. Biol.,* **2012**, *50*(7), 857-865.

[166] Oboh, G.; Ademiluyi, A.O.; Faloye, Y.M. Effect of combination on the antioxidant and inhibitory properties of tropical pepper varieties against α-amylase and α-glucosidase activities *in vitro*. *J. Med. Food,* **2011**, *14*(10), 1152-1158.

[167] Cazzola, R.; Camerotto, C.; Cestaro, B. Anti-oxidant, antiglycant, and inhibitory activity against α-amylase and α-glucosidase of selected spices and culinary herbs. *Int. J. Food Sci. Nutr.,* **2011**, *62*(2), 175-184.

[168] Islam, M.; Choi, H. Dietary red chilli (*Capsicum frutescens* L.) is insulinotropic rather than hypoglycemic in type 2 diabetes model of rats. *Phytother. Res.,* **2008**, *22*(8), 1025-1029.

[169] Islam, M.S.; Choi, H. Comparative effects of dietary ginger (*Zingiber officinale*) and garlic (*Allium sativum*) investigated in a type 2 diabetes model of rats. *J. Med. Food,* **2008**, *11*(1), 152-159.

[170] Striegel, L.; Kang, B.; Pilkenton, S.J.; Rychlik, M.; Apostolidis, E. Effect of black tea and black tea pomace polyphenols on α-glucosidase and α-amylase inhibition, relevant to type 2 diabetes prevention. *Front. Nutr.,* **2015**, *2*(3), 1-6.

[171] Chong-Ye, F.; Xuan-Jun, W.; HUANG, Y.W.; Shu-Mei, H.; SHENG, J. Caffeine is responsible for the bloodglucose-lowering effects of green tea and Puer tea extractsin BALB/c mice. *Chin. J. Nat. Med.,* **2015**, *13*(8), 595-601.

[172] Hong, L.; Yi, W.; Liangliang, C.; Juncheng, H.; Qin, W.; Xiaoxiang, Z. Hypoglycaemic and hypolipidaemic activities of sesamin from sesame meal and its ability to ameliorate insulin resistance in KK-Ay mice. *J. Sci. Food Agric.,* **2013**, *93*(8), 1833-1838.

[173] Lee, J.H.; Oh, M.K.; Lim, J.T.; Kim, H.G.; Lee, W.J. Effect of coffee consumption on the progression of type 2 diabetes mellitus among prediabetic individuals. *Korean J. Fam. Med.,* **2016**, *37*(1), 7-13.

[174] Devarajan, S.; Chatterjee, B.; Urata, H.; Zhang, B.; Ali, A.; Singh, R.; Ganapathy, S. A blend of sesame and rice bran oils lowers hyperglycaemia and improves the lipids. *The Am. J. Med.,* **2016**. [Epub ahead of print].

[175] Shidfar, F.; Rajab, A.; Rahideh, T.; Khandouzi, N.; Hosseini, S.; Shidfar, S. The effect of ginger (*Zingiber officinale*) on glycemic markers in patients with type 2 diabetes. *J. Complementary Integr. Med.,* **2015**, *12*(2), 165-170.

[176] Selvi, N.M.K.; Sridhar, M.; Swaminathan, R.; Sripradha, R. Efficacy of Turmeric as Adjuvant Therapy in Type 2 Diabetic Patients. *Indian J. Clin. Biochem.,* **2015**, *30*(2), 180-186.

[177] Wickenberg, J.; Ingemansson, L.S.; Hlebowicz, J. Effects of *Curcuma longa* (turmeric) on postprandial plasma glucose and insulin in healthy subjects. *Nutr. J.,* **2010**, *9*(1), 1.

[178] Tomé-Carneiro, J.; Larrosa, M.; Yáñez-Gascón, M.J.; Dávalos, A.; Gil-Zamorano, J.; Gonzálvez, M.; García-Almagro, F.J.; Ros, J.A.R.; Tomás-Barberán, F.A.; Espín, J.C. One-year supplementation with a grape extract containing resveratrol modulates inflammatory-related microRNAs

and cytokines expression in peripheral blood mononuclear cells of type 2 diabetes and hypertensive patients with coronary artery disease. *Pharmacol. Res.,* **2013**, *72*, 69-82.

[179] Arablou, T.; Aryaeian, N.; Valizadeh, M.; Sharifi, F.; Hosseini, A.; Djalali, M. The effect of ginger consumption on glycemic status, lipid profile and some inflammatory markers in patients with type 2 diabetes mellitus. *Int. J. Food Sci. Nutr.,* **2014**, *65*(4), 515-520.

[180] Mozaffari-Khosravi, H.; Talaei, B.; Jalali, B.A.; Najarzadeh, A.; Mozayan, M.R. The effect of ginger powder supplementation on insulin resistance and glycemic indices in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial. *Complement. Ther. Med.,* **2014**, *22*(1), 9-16.

[181] Khandouzi, N.; Shidfar, F.; Rajab, A.; Rahideh, T.; Hosseini, P.; Taheri, M.M. The effects of ginger on fasting blood sugar, hemoglobin a1c, apolipoprotein B, apolipoprotein aI and malondialdehyde in type 2 diabetic patients. *Iran. J. Pharm. Res.,* **2015**, *14*(1), 131-140.

[182] Fagherazzi, G.; Vilier, A.; Lajous, M.; Boutron-Ruault, M.C.; Balkau, B.; Clavel-Chapelon, F.; Bonnet, F. Wine consumption throughout life is inversely associated with type 2 diabetes risk, but only in overweight individuals: results from a large female French cohort study. *Eur. J. Epidemiol.,* **2014**, *29*(11), 831-839.

[183] Napoli, R.; Cozzolino, D.; Guardasole, V.; Angelini, V.; Zarra, E.; Matarazzo, M.; Cittadini, A.; Saccà, L.; Torella, R. Red wine consumption improves insulin resistance but not endothelial function in type 2 diabetic patients. *Metabolism.,* **2005**, *54*(3), 306-313.

[184] Mozaffari-Khosravi, H.; Ahadi, Z.; Tafti, M.F. The effect of green tea versus sour tea on insulin resistance, lipids profiles and oxidative stress in patients with type 2 diabetes mellitus: A randomized clinical trial. *Iran. J. Med. Sci.,* **2014**, *39*(5), 424-432.

[185] Liu, C.Y.; Huang, C.J.; Huang, L.H.; Chen, I.J.; Chiu, J.P.; Hsu, C.H. Effects of green tea extract on insulin resistance and glucagon-like peptide 1 in patients with type 2 diabetes and lipid abnormalities: a randomized, double-blinded, and placebo-controlled trial. *PLoS ONE,* **2014**, *9*(3), e91163.

[186] Parham, M.; Heidari, S.; Khorramirad, A.; Hozoori, M.; Hosseinzadeh, F.; Bakhtyari, L.; Vafaeimanesh, J. Effects of pistachio nut supplementation on blood glucose in patients with type 2 diabetes: a randomized crossover trial. *Rev. Diab. Stud., RDS,* **2013**, *11*(2), 190-196.

[187] Pan, A.; Sun, Q.; Manson, J.E.; Willett, W.C.; Hu, F.B. Walnut consumption is associated with lower risk of type 2 diabetes in women. *J. Nutri.,* **2013**, *143*(4), 512-518.

[188] Bahadoran, Z.; Tohidi, M.; Nazeri, P.; Mehran, M.; Azizi, F.; Mirmiran, P. Effect of broccoli sprouts on insulin resistance in type 2 diabetic patients: a randomized double-blind clinical trial. *Int. J. Food Sci. Nutr.,* **2012**, *63*(7), 767-771.

[189] Bahadoran, Z.; Mirmiran, P.; Hosseinpanah, F.; Hedayati, M.; Hosseinpour-Niazi, S.; Azizi, F. Broccoli sprouts reduce oxidative stress in type 2 diabetes: a randomized double-blind clinical trial. *Eur. J. Clin. Nutr.,* **2011**, *65*(8), 972-977.

[190] Thompson, S.V.; Winham, D.M.; Hutchins, A.M. Bean and rice meals reduce postprandial glycemic response in adults with type 2 diabetes: a cross-over study. *Nutr. J.,* **2012**, *11*(1), 1-7.

[191] Eldin, I.M.T.; Ahmed, E.M.; HM, A.E. Preliminary study of the clinical hypoglycemic effects of *Allium cepa* (red onion) in type 1 and type 2 diabetic patients. *Environ. Health Insights,* **2010**, *4*, 71.

[192] Hsu, C.H.; Liao, Y.L.; Lin, S.C.; Hwang, K.C.; Chou, P. The mushroom *Agaricus Blazei* Murill in combination with metformin and gliclazide improves insulin resistance in type 2 diabetes: a randomized, double-blinded, and placebo-controlled clinical trial. *J. Altern. Complement. Med.,* **2007**, *13*(1), 97-102.

[193] Banini, A.E.; Boyd, L.C.; Allen, J.C.; Allen, H.G.; Sauls, D.L. Muscadine grape products intake, diet and blood constituents of non-diabetic and type 2 diabetic subjects. *Nutrition,* **2006**, *22*(11), 1137-1145.

[194] da Silva Pinto, M.; de Carvalho, J.E.; Lajolo, F.M.; Genovese, M.I.; Shetty, K. Evaluation of antiproliferative, anti-type 2 diabetes, and antihypertension potentials of ellagitannins from strawberries (Fragaria× ananassa Duch.) using *in vitro* models. *J. Med. Food,* **2010**, *13*(5), 1027-1035.

[195] Koupý, D.; Kotolová, H.; Kučerová, J. Effectiveness of phytotherapy in supportive treatment of type 2 diabetes mellitus Billberry (*Vaccinium myrtillus*). *Ceska a Slovenska farmacie: casopis Ceske farmaceuticke spolecnosti a Slovenske farmaceuticke spolecnosti,* **2014**, *64*(1-2), 3-6.

[196] Parmar, H.S.; Jain, P.; Chauhan, D.S.; Bhinchar, M.K.; Munjal, V.; Yusuf, M.; Choube, K.; Tawani, A.; Tiwari, V.; Manivannan, E. DPP-IV inhibitory potential of naringin: an in silico, *in vitro* and *in vivo* study. *Diabetes Res. Clin. Pract.,* **2012**, *97*(1), 105-111.

[197] Nguyen, T.H.; Um, B.H.; Kim, S.M. Two Unsaturated Fatty Acids with Potent α-Glucosidase Inhibitory Activity Purified from the Body Wall of Sea Cucumber (Stichopus japonicus). *J. Food Sci.,* **2011**, *76*(9), H208-H214.

[198] Wikul, A.; Damsud, T.; Kataoka, K.; Phuwapraisirisan, P. (+)-Pinoresinol is a putative hypoglycemic agent in defatted sesame (*Sesamum indicum*) seeds though inhibiting α-glucosidase. *Bioorg. Med. Chem. Lett.,* **2012**, *22*(16), 5215-5217.

[199] Kuroda, M.; Mimaki, Y.; Nishiyama, T.; Mae, T.; Kishida, H.; Tsukagawa, M.; Takahashi, K.; Kawada, T.; Nakagawa, K.; Kitahara, M. Hypoglycemic effects of turmeric (*Curcuma longa* L. rhizomes) on genetically diabetic KK-Ay mice. *Biol. Pharm. Bull.,* **2005**, *28*(5), 937-939.