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# Plants and Natural Compounds with Antidiabetic Action

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**Abstract**

Diabetes has become the most common metabolic disease worldwide. In particular, type 2 diabetes is the most commonly encountered type of diabetes, which is characterised by the inability of the organism to respond to normal levels of circulating insulin, also called insulin resistance. Current antidiabetic therapy is based on synthetic drugs that very often have side effects. For this reason, there is a continuous need to develop new and better pharmaceuticals as alternatives for the management and treatment of the disease. Natural hypoglycaemic compounds may be attractive alternatives to synthetic drugs or reinforcements to currently used treatments. Their huge advantage is that they can be ingested in everyday diet. Recently, more attention is being paid to the study of natural products as potential antidiabetics. This mini review of the current literature is structured into three main sections focused on: (a) plant extracts, (b) plant biomolecules, and (c) other natural molecules that have been used for their antidiabetic effects. Potential molecular mechanisms of action are also discussed.

***Keywords:*** antidiabetic plants, antidiabetic natural biomolecules, type 2 diabetes

## Introduction

Diabetes is a metabolic disease that has become a serious problem of modern society due to the severe long-term health complications associated with it. In particular, type 2 diabetes mellitus (T2DM) is the most encountered form of diabetes, accounting for more than 80% of the total cases of diabetes (Berg *et al*., 2002; Cheța, 2010; Mlinar *et al*., 2007). Glucose metabolism disturbances are major factors leading to diabetes. The insulin released by the pancreatic β-cells is the hormone responsible for glucose homeostasis (Garrett and Grisham, 1999; Sesti, 2006). Insulin stimulates hepatocytes, myocytes, and adipocytes to uptake glucose from the circulatory system. Depending on need, glucose can either be used as an energetic source by glycolysis, or alternatively, stored as glycogen inside muscle or liver cells. The inappropriate utilization of insulin leads to insulin resistance, which is characterised by the inability of cells to respond to normal levels of circulating insulin (Berg *et al*., 2002; Cheța, 2010), thus leading to the occurrence of the disease.

Natural compounds may be feasible alternatives for the treatment of diabetes or reinforcements to currently used treatments. They may even reduce the risk of the disease. Large amounts can be consumed in everyday diet, which is a positive aspect. There are a large number of plants and natural biomolecules that have been discussed in literature for their antidiabetic effects. For example, plants have been used since ancient times to prevent conditions associated with diabetes (Soumyanath, 2003). The mechanism is most often not completely understood, but more and more studies are being conducted to elucidate the mechanisms of action of different plants and natural compounds. This mini review aims to discuss some key aspects related to the potential use of plants and natural biomolecules for the prophylaxis and treatment of type 2 diabetes as well as the potential mechanisms of action.

### *A. Plant Extracts with Antidiabetic Action*

There are more than 1000 plant species being used for the treatment of T2DM worldwide (Trojan-Rodrigues *et al*., 2011). In parts of the world where the population has restricted access to the healthcare system, the use of medicinal plants for the treatment of T2DM is widespread. In many cases, very little is known about the mechanism of action of traditionally used antidiabetic plants, thus preventing them from being used in standard diabetes care. Recently, more research is being focused on elucidating the action of these plants and their active constituents. Tab. 1 presents a number of plants that are currently used for their antidiabetic properties, together with their active biomolecules, based on recent studies.

*Gallega officinalis* has been used since ancient times in Europe for treating symptoms associated with T2DM (Whitters, 2001). It is now well established that its hypoglycaemic and insulin-sensitizing potential is associated with its guanide compound, galegine. This plant is still of great importance today despite the fact that the guanide compounds were discovered to be toxic for the human body. Related compounds such as the biguanide metformin molecule were later developed and are still widely used in antidiabetic therapy (Goldstein and Wieland, 2008).

Brazil is one country where a significant percent of the total population uses plants as antidiabetics. In their re-

cent review, Trojan-Rodrigues *et al*. (2011) list 81 plant species from 42 families that are being used for diabetes care in the Brazilian state of Rio Grande do Sul. The most studied species for their effects are shown in Tab. 1. Alarcon-Aguilara *et al*. (1998) performed a screening study on 28 medicinal plants used in Mexico for T2DM treatment and found eight of them (Tab. 1) to exert hypoglycaemic effects. Aslan *et al*. (2010) tested plants used as part of the diet and as antidiabetics in Turkey. They found that *Cydonia oblonga* Mill. and *Allium porrum* L. possessed potent antidiabetic effects.

Administration of *Swertia punicea* extract and the methylswertianin and bellidifolin fractions of the extract to type 2 diabetic mice improved insulin sensitivity (Tian *et al*., 2010). The mechanism involved increased expression of key proteins (insulin receptor (IR), insulin receptor substrate-1 (IRS-1), and phosphatidylinositol 3-kinase (PI3K)) that are involved in the insulin signalling processes. Additionally, methylswertianin and bellidifolin decreased the activity of glucokinase (GK) and increased the activity of glucose-6-phosphatase (G6Pase), enzymes that are involved in the secretion of insulin from pancreatic β-cells. Similar mechanisms of action leading to increased phosphorylation of IR and IRS-1, together with increased glucose transporter 4 (GLUT4) and PI3K mRNA expression in the L6 cells, were observed by Kanaujia *et al*. (2010) after administration of the fruit extract of *Capparis moonii*. The effect was attributed to the presence of two gallotannins with insulin-mimetic activity in the extract.

*Artemisia dracunculus* L. has been reported to have hypoglycaemic effects by several researchers (Ribnicky *et al*., 2009; Wang *et al*., 2011). Wang *et al*. (2011) found that *Artemisia dracunculus* L. improved insulin sensitivity and IR signaling in insulin-resistant KK-Ay mice models. They could not explain the cellular mechanisms behind the effect. One suggestion given was the modulation of skeletal muscle protein degradation and phosphatase activity. Logendra *et al*. (2006) isolated 4,5-di-O-caffeoylquinic acid, 6-demethoxycapillarisin, and 2',4'-dihydroxy-4-methoxydihydrochalcone from the ethanolic extract of *Artemisia dracunculus* L. The compounds showed inhibitory effects towards the enzyme aldose reductase, a key enzyme involved in diabetic complications, which may explain the antidiabetic effect. The bioactive compounds in *Artemisia dracunculus* L. also include davidigenin, sakuranetin, and 5-O-caffeoylquinic acid (Eisenman *et al*., 2011).

*Salacia reticulata* has been traditionally used for the treatment of T2DM in countries such as Sri Lanka, India, and Thailand. From this plant, Muraoka *et al*. (2008) isolated α-glucosidase inhibitors, such as salacinol, kotalanol, de-O-sulphated-salacinol, and de-I-sulphated-kotalanol, the inhibitory effects of which are similar to that of voglibose and acarbose, which are widespread antidiabetic drugs (see section C). α-glucosidase is an enzyme that catalyses the decomposition of disaccharides to glucose. Any inhibitory effect from an external stimulus towards α-glucosidases leads to the retardation of their action, consequently becoming an effective approach for the treatment of T2DM (Goldstein and Wieland, 2008). Currently, there is a whole class of antidiabetic drugs that function as α-glucosidase inhibitors.

Other α-glucosidase inhibitors were also found in *Morus alba*, another natural antidiabetic plant. The α-glucosidase inhibitory effect of *Morus alba* was also observed in studies on Caco-2 cell cultures (Hansawasdi and Kawabata, 2006). Yang *et al*. (2012) found 15 bioactive molecules (Tab. 1) with α-glucosidase and tyrosinase inhibitory effects in the leaf extracts of *Morus alba* containing the following compounds: flavanes, prenylated stilbenes, and iminosugars. Katsube *et al*. (2006) also identified the presence of flavonol glycosides (see also section B), another class of antioxidant compounds with antidiabetic potential.

A number of culinary herbs from Thailand (Wongsa *et al*., 2012) were tested for total phenolic content, antioxidant activity (by the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical inhibition assay), and α-amylase and α-glucosidase potential inhibition activity. It was found that *Solanum xanthocarpum*, *Ocimum sanctum*, and *Acacia pennata* could be used in the dietary management of T2DM due to their high contents of polyphenolics, caffeic acid, and p-coumaric acid. *Acacia pennata* had the strongest effect on α-amylase inhibition; the presence of caffeic acid was correlated with this effect. α-glucosidase inhibition was linked to the total phenolic content. Other plants with the α-glucosidase inhibitor effect are *Macaranga tanarius* (Puteri and Kawabata, 2010), *Salacia oblonga*, *Salacia chinensis* (Giron *et al*., 2009; Muraoka *et al*., 2010), *Eleutherine americana* (Ieyama *et al*., 2011), *Aquilaria sinensis* (Feng *et al*., 2011), and *Panax japonicus* (Chan *et al*., 2010).

In a study on type 2 diabetic mice, administration of *Curcuma longa* L. rhizomes extract led to the activation of the peroxisome proliferator-activated receptor-γ (PPAR-γ) (Kuroda *et al*., 2005) through the ligand binding activity of the extract towards the receptor. PPAR-γ is a key receptor in lipid and glucose homeostasis because of its ability to reduce the plasma free fatty acids (FFAs) (Bajaj *et al*., 2007; Kasuga *et al*., 2007; Nunn *et al*., 2007). The receptor is currently used as a target for the treatment of T2DM (Goldstein and Wieland, 2008); the antidiabetic thiazolidinediones drugs exert their insulin sensitizing action through their high affinity for the receptor PPAR-γ. Thus, *Curcuma longa* is a promising therapeutic agent in the prevention and/or amelioration of T2DM. Lee *et al*. (2008) tested a combined hypoglycaemic mixture of *Melissa officinalis* L., *Morus alba* L., and *Artemisia capillaris* Thunb that resulted in changes in the expression of the PPAR-α, another key receptor in lipid and lipoprotein metabolism.

*Urtica dioica* is another example of a hypoglycaemic plant. *In vivo* studies on diabetic rats (Bnouham *et al*., 2003) showed an increase in blood insulin levels and

Tab. 1. Examples of some plants with confirmed antidiabetic properties

| Plant | Used part | Active compounds | Type of study | Preparation | References |
|---|---|---|---|---|---|
| *Gallega officinalis* | leaves, seeds | galegine | diabetic rats | aqueous extract | Whitters, 2001; Goldstein and Wieland, 2008; Lemus *et al.*, 1999 |
| *Syzygium cumini* | seeds, leaves, flower | mycaminose | diabetic rats | ethanolic extract | Trojan-Rodrigues *et al.*, 2011; Kumar *et al.*, 2008 |
| *Bauhinia forficata* | leaves, flowers, bark | kaempferol-3-neohesperidoside (insulin mimetic) | rat soleus muscle | ethanolic extract | Trojan-Rodrigues *et al.*, 2011; Cazarolli *et al.*, 2009 |
| *Bidens pilosa* L. | whole plant | polyacetylenic glucosides | diabetic mice rat pancreatic islets | aqueous extract | Trojan-Rodrigues *et al.*, 2011; Hsu *et al.*, 2009 |
| *Swertia punicea* | whole plant | methylswertianin, bellidifolin | diabetic mice | ethanol extract ethyl-acetate extract | Tian *et al.*, 2010 |
| *Capparis moon* | fruits | gallotannins (chebulinic acid derivatives) | L6 cells | ethanolic extract | Kanaujia *et al.*, 2010 |
| *Artemisia dracunculus* L. | whole plant | davidigenin, sakuranetin, 2',4'-dihydroxy-4-methoxydihydrochalcone, 4,5-di-O-caffeoylquinic acid, 5-O-caffeoylquinic acid, 6-demethoxycapillarisin | diabetic mice | ethanolic extract | Wang *et al.*, 2011; Ribnicky *et al.,* 2009; Eisenman *et al.*, 2011; Logendra *et al.,* 2006 |
| *Salacia reticulata* | root, stem | Salacinol, kotalanol, de-O-sulfated salacinol, de-O-sulfated kotalanol, ponkolanol, salaprinol | compound isolation, identification | aqueous extract | Muraoka *et al.,* 2008 |
| *Morus alba* | leaves | (2S)-euchrenone, chalcomoracin, moracin C, moracin D, moracin N, (2R)/(2S)-euchrenone, moracin N , quercetin, norartocarpetin, several flavanes | compound isolation, identification | ethanolic extract | Yang *et al.,* 2012 |
| *Morus alb*a | leaves | quercetin 3-(6-malonylglucoside), rutin (quercetin 3-rutinoside), isoquercitrin (quercetin 3-glucoside) | Caco-2 cells | ethanolic extract aqueous extract | Hansawasdi and Kawabata, 2006; Katsube e*t al.*, 2006 |
| *Ocimum sanctum* | leaves | polyphenols, caffeic acid, p-coumaric acid | *in vitro* | aqueous extract | Wongsa *et al.*, 2012 |
| *Acacia pennata* | shoot tips | polyphenols, caffeic acid | *in vitro* | aqueous extract | Wongsa *et al.*, 2012 |
| *Solanum xanthocarpum* | fruit | polyphenols, caffeic acid | *in vitro* | aqueous extract | Wongsa *et al.*, 2012 |
| *Macaranga tanarius* | seeds | ellagitannins (mallotinic acid, corilagin, chebulagic acid, macatannins A and B) | compound isolation, identification | ethanolic extract | Puteri and Kawabata, 2010 |
| *Salacia oblonga* *Salacia chinensis* | root, stem, leaves | salacinol, kotalanol, mangiferin | compound isolation, identification | aqueous extract | Muraoka *et al.*, 2010; Giron *et al.*, 2009 |
| *Eleutherine americana* | bulb | eleutherinoside A | compound isolation, identification | methanolic extract | Ieyama *et al.*, 2011 |
| *Aquilaria sinensis* | leaves | mangiferin, iriflophenone 2-*O*-α-L-rhamnopyranoside, iriflophenone 3-*C*-β-D-glucoside, iriflophenone 3,5-*C*-β-D-diglucopyranoside | compound isolation, identification | ethanolic extract | Feng *et al.*, 2011 |
| *Panax japonicus* | root | polyacetylenes, phenolic compounds, one sesquiterpenoid, one sterol glucoside | compound identification | ethanolic extract | Chan *et al.*, 2010 |

Tab. 1. Examples of some plants with confirmed antidiabetic properties (cont.)

| Plant | Used part | Active compounds | Type of study | Preparation | References |
|---|---|---|---|---|---|
| *Curcuma longa* | rhizome | curcumin, demethoxycurcumin, bisdemethoxycurcumin, ar-turmerone | diabetic mice<br>*in vitro* | ethanolic extract | Kuroda *et al.*, 2005 |
| *Rhododendron tomentosum*<br>*Picea mariana* | fruit | quercetin | Caco-2 cells<br>diabetic rats | ethanolic extract | Nistor Baldea *et al.*, 2010 |
| *Aronia melanocarpa* | fruit | anthocyanins | diabetic rats | fruit juice | Kulling and Rawel, 2008; Valcheva-Kuzmanova *et al.*, 2007 |
| *Stevia rebaudiana* | leaves | alkaloids, flavonoids | diabetic rats | aqueous extract | Kujur *et al.*, 2010 |
| *Nigella sativa* | seeds | gallic acid, (–)-*p*-hydroxybenzoic acid, chlorogenic acid, vanillic acid, *p*-coumaric, ferulic acid, *trans*-2-hydroxycinnamic acid, *trans*-cinnamic acid, epicatechin, (+)-catechin, quercetin, apigenin, amentoflavone, flavone | diabetic rats | crude aqueous extract<br>methanolic extract | Bourgou *et al.,* 2008; Meddah *et al.,* 2009 |
| *Eucalyptus globules* | leaves | | diabetic rats | ethanolic extract | Ahlem e*t al.*, 2009 |
| *Phaseolus vulgaris L.* | seeds | alkaloids, flavonoids, fiber, proteins, tannins, terpenoids, saponins, quercetin, anthocyanin, catechin | diabetic rats | extract | Ocho-Anin Atchibri *et al.*, 2010 |
| *Marrubium vulgare* | aerial part | flavonoids | diabetic rats | methanolic extract | Elberry *et al.*, 2011 |
| *Ruta graveolens* | leaves | rutin | diabetic rats | aqueous extract | Ahmed *et al.*, 2010 |
| *Carissa carandas* | fruit | gallic acid, flavonoids | diabetic rats | ethanol extract | Itankar *et al.*, 2011 |
| *Pinus pinaster* | bark | polyphenols: proanthocyanidins, catechin, epicatechin | Caco-2 cells<br>Diabetic rats<br>T2DM human patients | Aqueous extract | El-Zein *et al.*, 2011; Bedekar *et al.*, 2010; Liu *et al.*, 2004 |
| *Piper retrofractum* | fruits | piperidine alkaloids: piperine, pipernonaline,dehydropipernonaline | 3T3-L1 adipocytes<br>L6 myocytes | Ethanol extract | Kim *et al.*, 2011 |

decrease in blood glucose levels upon administration of *Urtica dioica* extracts. According to Nistor Baldea *et al*. (2010), *Rhododendron tomentosum* and *Picea mariana* exert inhibitory effects on the intestinal glucose absorption, both *in vitro* and *in vivo*, and decrease the expression of the Na+-dependent glucose transporter (SGLT1) and glucose transporter 2 (GLUT2) proteins in CaCo-2/15 cell lines, indicating that these plants can be useful in diabetes prevention and care.

*Aronia melanocarpa* berries possess numerous biological and medicinal effects (Kulling and Rawel, 2008). They are rich in phenolic antioxidants, especially anthocyanins. Valcheva-Kuzmanova *et al*. (2007) have investigated the influence of *Aronia melanocarpa* fruit juice on plasma glucose and lipid levels in diabetic streptozotocin rats. The administration of *Aronia* fruit juice lowered the glucose and triglyceride levels in diabetic rats. Additionally, in a human study, the daily intake of *Aronia* juice over a period of 3 months was effective in lowering fasting glucose levels in patients with type 2 diabetes (Kulling and Rawel, 2008). *Aronia melanocarpa* fruit juice may become useful in the treatment of diabetes mellitus and its associated complications. *In vivo* studies and clinical trials must be conducted to validate *in vitro* results related to the action of anthocyanins and anthocyanidins.

By conducting *in vitro* experiments on rat pancreatic β-cells using *Cornus officinalis* extracts, Chen *et al*. (2008) found that the extracts possessed insulin-mimetic activity and stimulated β-cell function by enhancing insulin secretion and protecting β-cells against toxic damage. Administration of *Stevia rebaudiana* extracts (Kujur *et al*., 2010) led to decreased blood glucose levels in diabetic rats. With regards to the mechanism of action, it is suggested that the counteraction of glucotoxicity in the pancreatic β-cells or the suppression of glucagon secretion by α-pancreatic cells could be involved (glucagon normally raises glucose levels in the blood).

Seed extracts of *Nigella sativa* have many therapeutic purposes relevant for antidiabetic use. Meddah *et al*. (2009) studied the effect of the crude aqueous extract of *Nigella sativa* seeds on intestinal glucose absorption. *Nigella sativa* inhibited the intestinal absorption of glucose, supporting its use as an antidiabetic compound. Other examples of plants with antidiabetic properties that were studied and confirmed by literature studies include the following: *Eucalyptus globules* (Ahlem *et al*., 2009), *Phaseolus vulgaris* L. (Ocho-Anin Atchibri *et al*., 2010), *Marrubium vulgare* (Elberry *et al*., 2011), *Coriandrum sativum* L. (Aissaoui *et al*., 2011), *Swertia punicea* (Tian *et al*., 2010), *Viscum album* (Ohran *et al*., 2005), *Brassica juncea* (Thirumalai *et al*., 2011), *Salvia officinalis* L. (Eidi *et al*., 2005), *Ruta graveolens* (Ahmed *et al*., 2010), *Carissa carandas* (Itankar *et al*., 2011), *Pinus pinaster* (Bedekar *et al*., 2010; El-Zein *et al*., 2011), *Punica granatum* (Bagri *et al*., 2009), and *Piper retrofractum* (Kim *et al*., 2011).

*B. Natural Plant Biomolecules with Antidiabetic Action*

Synthetic drugs currently in use for diabetes treatment sometimes have side effects (Goldstein, 2008; Stumvoll *et al*., 2005). For this reason, natural hypoglycaemic compounds present an attractive alternative to synthetic drugs or as reinforcements for currently used treatments (Kimura, 2006; Rout *et al*., 2009). This section presents some of the literature findings related to antidiabetic plant biomolecules, with particular emphasis on large classes of compounds that are easily available from many plant sources. Tab. 2 shows the different classes of plant compounds with antihyperglycaemic activity, together with few examples from each class.

A large number of hypoglycaemic compounds have antioxidant properties. Among the trigger factors for T2DM, oxidative stress has a well-established role (Goldstein and Wieland, 2008). Oxidative stress leads to the formation of free radical species, which in turn negatively affect vital cellular processes. The antioxidant properties of natural compounds may be acting synergistically with their hypoglycaemic activity in exerting an overall antidiabetic action.

Polyphenolic compounds, especially flavonoids, are among the classes of compounds that have received the most attention (Soumyanath, 2003) with regard to their antidiabetic properties. Flavonoids are natural polyphenolic molecules of plant origin known for their antioxidant, anti-inflammatory, and anticarcinogenic properties (Pinent *et al*., 2008). Dietary intake of flavonoids might prove to be important for alternative diabetes treatments or reduction of the risk of the disease. Attempts have been made to determine their potential in preventing β-cell apoptosis, promoting β-cell proliferation and insulin secretion (Pinent *et al*., 2008), and enhancing insulin activity (Ahmed *et al*., 2010). Through *in vitro* and *in vivo* studies, Ahmed *et al*. (2010) were able to demonstrate that the pharmacologically active compound of *Ruta graveolens*, the flavonoid rutin, had the ability to positively influence insulin activity and insulin resistance in type 2 diabetic rats. Their results showed that rutin decreased glycaemia, lipidaemia, serum insulin concentrations, liver glycogen content, and hexokinase activities. Rutin was also effective in increasing the expression of the receptor PPAR-γ, leading to improved muscle insulin sensitivity and insulin signaling by increasing insulin-stimulated GLUT4 receptor activity (Petersen *et al*., 2006) (GLUT4, known as glucose receptor 4, is the receptor that accounts for most of the insulin-stimulated glucose uptake in muscles and adipose tissue cells (Kobayashi *et al*., 2004)). Catechin, a flavan-3-ol, was also identified as a modulator of insulin secretion (Chemler *et al*., 2007).

Isoflavones, commonly known as phytoestrogens may also act as potential antidiabetics; for example, genistein, ingested in soy products at dietary concentrations, increased glucose-stimulated insulin secretion in cell lines and mouse pancreatic islets (Fu and Liu, 2009; Liu *et al*.,

Tab. 2. Classes of reported antidiabetic compounds and some examples from each class

| Classes of compounds | | Compounds |
|---|---|---|
| Flavonoids | Anthocyanidins | cyanidin, delphynidin, petunidin, peonidin, pelargonidin, malvidin |
| | Anthocyanins | anthocyanidins+sugar residue (glucose, galactose, arabinose, rhamnose, xylose) e.g. cyanidin 3-glucoside, cyanidin 3-galactoside, pelargonidin-3-arabinoside |
| | Flavones | Flavonols: quercetin, kaempferol, myricetin, isorhamnetin, rutin (quercetin-3-O-rutinoside), kaempferol-3-neohesperidoside, isoquercitrin (quercetin 3-glucoside), apigenin |
| | | Flavanones: sakuranetin |
| | | Flavanonol: taxifolin (dihidroquercetin), dihidrokaempferol |
| | Isoflavones | genistein |
| | Flavan-3-ols | catechins (proanthocyanidins), epicatechins |
| | Isoflavonoids | phytoestrogens |
| Chalcones | | davidigenin, 2',4'-dihydroxy-4-methoxydihydrochalcone |
| Tannins | | gallotannins: 1,3,6-tri-O-galloyl-2-chebuloyl-β-D-glucopyranoside; 1,3,6-tri-O-galloyl-2-chebuloyl ester-β-D-glucopyranoside ellagitannins: mallotinic acid, corilagin, chebulagic acid, macatannins A and B |
| Xanthones | | mangiferin, bellidifolin, swerchirin, methylswertianin |
| Organic acids | | kaurenoic acids, p-coumaric acid, vanillic acid, gallic acid, *p*-hydroxybenzoic acid |
| Cinamic acid derivatives | | caffeic acid, ferulic acid, chlorogenic acid |
| Sugars | | salacinol, kotalanol, ponkolanol, salaprinol |
| Curcuminoids | | curcumin, demethoxycurcumin, bisdemethoxycurcumin |
| Alkaloids | | conophylline, piperine, pipernonaline, dehydropipernonaline |

2006). The mechanism of their action involved the activation of the cAMP/PKA (cyclic adenosine monophosphate/protein kinase A) signaling cascade, which led to an increase in intracellular $Ca^{2+}$, leading to the stimulation of insulin secretion.

As discussed above, reactive oxygen species are among the trigger factors for insulin resistance (Guichard *et al*., 2008; Houstis *et al*., 2006; Rahimi *et al*., 2005; Song *et al*., 2006). This is one more reason why antioxidant therapies are promising for the treatment of T2DM. Kaempferol, a plant flavonol, was recently tested on HIT-T15 by Lee *et al*. (2010). They found that kaempferol molecules protected the cells against the apoptosis induced by oxidative stress.

Anthocyanins, another subclass of flavonoids, are red or violet colored polyphenolics with high antioxidant potential. They are composed of an aglycone (polyphenolic anthocyanidin) and a sugar residue. Anthocyanins play a vital role in the prevention of neuronal and cardiovascular diseases, cancer, and diabetes (Castañeda-Ovando *et al*., 2010). Anthocyanin-containing fruits are sometimes used as complementary antidiabetic preparations (Castañeda-Ovando *et al*., 2010; Jayaprakasam *et al*., 2005). For example, cyanidin 3-glucoside, an anthocyanin from black rice, exhibited a protective effect on insulin sensitivity in experiments on insulin-resistant adipose tissue cells induced by hydrogen peroxide ($H_2O_2$) or tumour necrosis factor α (TNF-α) (Guo *et al*., 2008). It is known that both $H_2O_2$ and the inflammatory TNF-α molecule inhibit the process of insulin signaling (Sesti, 2006). The exposure to $H_2O_2$ or TNF-α leads to IRS serine phosphorylation concurrent with a decrease in insulin-stimulated IRS tyrosine phosphorylation and a decrease of cellular glucose uptake. Cyanidin 3-glucoside exerts its protective role by reducing the intracellular production of the reactive oxygen species and attenuating the unwanted effects due to $H_2O_2$ or TNF-α in a dose-dependent way by a mechanism that involves the inhibition of c-Jun $NH_2$-terminal kinase. The effect of an anthocyanin-rich extract from black rice was also studied on fructose-fed rats exhibiting high plasma insulin levels and low insulin sensitivity (Guo *et al*., 2007). The effects were compared to those of pioglitazone, a prescription drug for T2DM. Administration of the anthocyanin-rich extract prevented the development of fructose-induced insulin resistance. Additionally, the treatment with the anthocyanin-rich extract ameliorated glucose intolerance and hyperlipidaemia, as pioglitazone did, but the extract failed to reverse fructose-induced hyperinsulinaemia. The underlying mechanism may be related to inhibition of oxidative stress and improvement of the plasma lipid profile.

Activation of the nuclear factor NF- κB is a key signalling mechanism for pancreatic β-cell damage that is connected to insulin resistance. NF-κB controls the transcription process for different genes; it is involved in cellular responses to different stimuli such as stress, cytokines, and free radicals. It is normally held in its inactive form by being bound to the inhibitory IκB molecule. However, it may be activated if IκB undergoes phosphorylation by I-Kappa-B kinase (IKK), leading to the release and activation of NF-κB that may induce pancreatic β-cell damage (Song *et al*., 2010; Stumvoll *et al*., 2005). The activation of the nuclear factor NF-κB by stress factors (cytokine molecules and free radicals) is strongly connected to β-cell damage. Sulphuretin extracted from *Rhus verniciflua* was found to

inhibit cytokine- or streptozotocin-induced damage in rat insulinoma β-cells and in isolated cells that induced toxicity (Song *et al*., 2010).

Anthocyanin-rich extracts obtained from blueberries exhibited hypoglycaemic effects in diabetic mice. The hypoglycaemic activity was comparable to that of the known antidiabetic drug metformin (Grace *et al*., 2009). Jayaprakasam *et al*. (2005) performed *in vitro* studies on rodent pancreatic β-cells and found that anthocyanins, such as cyanidin-3-glucoside, delphinidin- 3-glucoside, and pelargonidin-3-galactoside, as well as the anthocyanidin pelargonidin were efficient in stimulating insulin secretion from pancreatic β-cells. The stimulation of insulin secretion is also the mechanism of action of oral hypoglycaemic agents used in diabetes therapy such as sulfonylurea-based drugs that directly stimulate insulin release from β-cells of type 2 diabetic patients. Sulfonylurea-based drugs have the disadvantage of failing to control normal blood glucose levels, and this is the reason behind why anthocyanins may serve as a natural alternative treatment.

Some anthocyanin-rich plant extracts have inhibitory effects towards α-glucosidase and α-amylase (Bedekar *et al*., 2010; Matsui *et al*., 2001). Matsui *et al*. (2001) tested different extracts towards α-glucosidase inhibition and found that some of the extracts had α-glucosidase and α-amylase inhibitory effects. However it was not entirely clear whether the effect was caused by the anthocyanins or other compounds from the extract.

Because anthocyanins and anthocyanidins are not harmful in any way to humans, it is important to evaluate their clinical efficacy in the prevention and treatment of T2DM.

Apart from the biomolecules discussed above, there are many more flavonoids mentioned in the literature for their hypoglycaemic effect: rhamnocitrin-3-O-isorhamninoside, rhamnetin-3-O-isorhamninoside, apigenin (Ammar *et al*., 2009), apigenin 6-neohesperidose, kaempferol 3-robinobioside, kaempferol 3-rutinoside (Abraham *et al*., 2008), luteolin-7-O-glucoside, apigenin-7-O-glucoside (Bansal *et al*., 2011), and quercetin (Coskun *et al*., 2005; Tapas *et al*., 2008).

Kojima and Umezawa (2006) performed experiments on pancreatic AR42J cells (a model of pancreatic progenitor cells) and on rats with induced diabetes. They found that conophylline, an alkaloid compound extracted from the leaves of the tropical plant *Ervatamia microphylla*, was effective in stimulating the differentiation of progenitor cells into β-cells. Conophylline also induced differentiation in cultured pancreatic progenitor cells obtained from foetal and neonatal rats. Conophylline increased the expression of neurogenin-3 by activating p38 mitogen-activated protein kinase and thereby induced differentiation of AR42J cells. Additionally, conophylline was effective in reversing hyperglycaemia in neonatal streptozotocin-treated rats; both the insulin content and the β-cell mass were increased by conophylline. Other alkaloid compounds isolated from *Piper retrofractum*, such as piperine, pipernonaline, and dehydropipernonaline, activated AMP-activated protein kinase (AMPK) signaling and the PPAR-γ protein (Kim *et al*., 2011) in 3T3-L1 adipocytes and L6 myocytes, suggesting potential antidiabetic effects.

Pygnogenol, the patented name of the pine bark (*Pinus pinaster*) extract, possesses antidiabetic effects (Bedekar *et al*., 2010; El-Zein *et al*., 2011). The extract contains bioactive compounds, namely proanthocyanidins (dimers or oligomers of catechin and epicatechin and their gallic acid esters), the flavonoids catechin and epicatechin, ferulic and caffeic acids, and taxifolin (Bedekar *et al*., 2010). The mechanism of action of pygnogenol is still not entirely clear. El-Zein *et al*. (2011) studied its effect on Caco-2 cells; it decreased intestinal glucose transport. Their work suggested that the mechanism involves decreasing the number of glucose transporters (GLUT2) by processes that lead to activation of p38 mitogen-protein kinase (p38 MAPK) and PI3K, thus affecting the insulin signaling pathway. Another study (Schäfer and Högger, 2007) claimed that the oligomeric proanthocyanidins from the pine bark extract have a higher α-glucosidase inhibitory effect than acarbose, a commonly used antidiabetic α-glucosidase inhibitor.

Ellagitannins are another class of plant biocomolecules that inhibit α-glucosidase enzymes (McDougall and Stewart, 2005; Puteri and Kawabata, 2010). Sugar-like structures, more precisely thiosugars such as kotalanol (Xie *et al*., 2011a), salacinol (Muraoka *et al*., 2010), neoponkoranol, neosalaprinol (Xie *et al*., 2011b), and de-O-sulphated-kotalanol (Muraoka *et al*., 2008), also have α-glucosidase inhibitory effects that are sometimes comparable to that of the prescription drugs acarbose and voglibose. Similar effects are also reported for the alkaloids nummularine-R, nummularin-C, and hemsine-A (Choudhary *et al*., 2011); some polyacethylenes and saponins (Chan *et al*., 2010); polyphenolic compounds such as iriflophenone 2-O-α-L-rhamnopyranoside, iriflophenone 3-C-β-D-glucoside, iriflophenone-3,5-C-β-D-diglucopyranoside (Feng *et al*., 2011), eleutherinoside , and eleuthoside (Ieyama *et al*., 2011); and bromophenols such as 2,4,6-tribromophenol and 2,4-dibromophenol (Kim *et al*., 2011).

The xanthone compound mangiferin is another natural molecule with hypoglycaemic properties (Soumyanath, 2006). According to Giron *et al*. (2009), mangiferin, the bioactive compound of the *Salacia oblonga* extract, increases the expression of GLUT4 glucose transporters and their translocation to the cell membrane in L6-myocites and 3T3-adipocytes, thus stimulating glucose uptake by the cells.

In a recent study, Gandhi *et al*. (2011) found that methyl caffeate administered to diabetic rats had a hypoglycaemic effect caused by an increased expression of the GLUT4 receptor and regeneration of the pancreatic β-cells.

The use of inhibitors of 11β-hydroxysteroid dehydrogenase-1 is a novel approach in the management of T2DM (Tahrani *et al*., 2011). Potential inhibitors for 11β-hydroxysteroid dehydrogenase-1 were also sought out in flavonoid compounds. Torres-Piedra *et al*. (2010) tested several flavonoids on human embryonic kidney (HEK293) cells and found that quercetin and flavone had inhibitory effects on the 11β-hydroxysteroid dehydrogenase-1 enzyme. The effect is thought to be related to the interaction with the catalytic active site of 11β-hydroxysteroid dehydrogenase-1. However, more studies are required to elucidate the exact mechanism and to identify novel plant compounds that can act as 11β-hydroxysteroid dehydrogenase-1 inhibitors.

*C. Other Natural Biomolecules with Antidiabetic Action*

Compounds such as acarbose, miglitol, and voglibose (Fig. 1) are a few examples of natural compounds of microbial origin that are currently used in the treatment of T2DM (Bedekar *et al*., 2010; Goldstein and Wieland, 2008). All these compounds act as α-glucosidase inhibitors and are used in T2DM therapy, especially in Central and South Europe and Asia (Goldstein and Wieland, 2008). Acarbose is a pseudotetrasaccharide, a secondary metabolite produced by the bacterium species *Actinoplanes* sp. SE50. Miglitol and voglibose both contain only one sugar ring. Miglitol is synthesised from D-glucose by *Glucanobactor oxydans*, while voglibose is synthesised from valilamine that is obtained from the fermentation of *Streptomyces* culture broth.

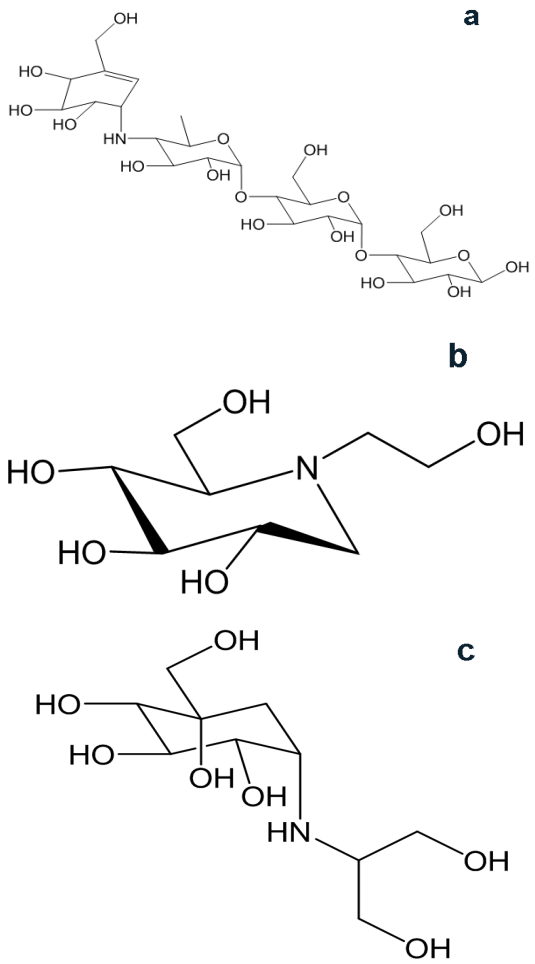


Fig. 1. Molecular structures of the (a) acarbose, (b) miglitol, and (c) voglibose

Their inhibitory effects on the α-glucosidase enzyme offer ways to control the release of glucose from carbohydrates. Basically, the inhibition reduces the degradation of carbohydrates, leading to poor carbohydrate metabolisation and digestion. Due to their high affinity for α-glucosidases, the inhibitors block the enzyme from binding to the carbohydrates, resulting in a decreased ability to metabolise the complex sugars to monosaccharides, therefore decreasing the glucose concentration. Acarbose inhibits both α-glucosidases and pancreatic α-amylases enzymes; voglibose has little effect on α-amylases, while miglitol shows no effect (Goldstein and Wieland, 2008) (pancreatic α-amylases catalyse the digestion of complex starches to oligosaccharides, while α-glucosidases such as sucrases, maltases, isomaltases hydrolise oligosaccharisdes, trisaccharides, and disaccharisdes into monosaccharides). Acarbose, miglitol, and voglibose show different inhibitory effects on α-glucosidases. Acarbose is most effective on glucoamylase, followed by sucrase, maltase, and dextranase. Miglitol is a more potent inhibitor sucrase and maltase than acarbose; it is also active on isomaltase but shows no effect on α -amylase. Voglibose has a strong α-glucosidase inhibitory effect but little effect on α -amylase.

**Conclusions**

Natural products such as plant extracts, phytochemicals, and microbial metabolites are attracting more and more attention for their potential uses in the treatment and prevention of type 2 diabetes mellitus. A number of plant extracts and natural biomolecules that have been tested for their antidiabetic properties using both *in vivo* and *in vitro* approaches were reviewed here. Some of them show very promising effects, which indicate that the dietary intake of phytochemicals could be a promising strategy for diabetes prevention. Additionally, therapies based on phytochemicals could constitute a novel pharmacological approach for treatment or an approach that would reinforce existing treatments.

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