International Journal of Food Sciences and Nutrition,
2011; Early Online: 1–11

informa
healthcare

Functional food and diabetes: A natural way in diabetes prevention?

SIMONETTA BALLALI[1] & FEDERICO LANCIAI[2]

[1]*Prochild ONLUS, Trieste (TS), Italy, and* [2]*Food Research and Innovation srl, Campodarsego (PD), Italy*

Abstract
Diabetes shows a wide range of variation in prevalence around the world and it is expected to affect 300 million by the year 2025. In a prevention framework where banning policies and educational strategies lead the interventions, functional foods (FFs) with their specific health effects could, in the future, indicate a new mode of thinking about the relationships between food and health in everyday life. Functional ingredients, such as stevioside, cinnamon, bitter melon, garlic and onion, ginseng, *Gymnema sylvestre* and fenugreek, have been addressed for their specific actions towards different reactions involved in diabetes development. New strategies involving the use of FF should be validated through large-scale population trials, considering validated surrogate end points to evaluate the effect of FF in prevention of chronic diseases such as type 2 diabetes mellitus.

Keywords: *diabetes, prevention, functional food, stevioside, cinnamon*

Background

The term diabetes mellitus (DM), usually referred to simply as diabetes, describes a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. It is associated with severe long-term complications, such as retinopathy, nephropathy, neuropathy, myocardial infarction, cerebral embolism and blood vessels damages.

DM shows a wide range of variation in prevalence around the world, being almost absent in New Guinea whereas DM interests half of Pima Indian population (Pradeepa and Mohan 2002). The World Health Organization (WHO) estimated that in 1995, 135 million people were diabetics, with a forecast increase till 300 million by the year 2025 (WHO 2008). In the context of this worldwide epidemic of obesity and type 2 diabetes mellitus (T2DM), more than 75% of the patients are in developing countries. India sets itself as the country with the largest number of diabetics (Yoon et al. 2006), with a prevalence of diabetes among urban Indians of 2.1% in 1970s, which has reached nowadays to 12.1% (Pradeepa and Mohan 2002). Regarding developed countries, such as Europe and the USA, the increasing trend is mainly due to the prolonged survival of both the general and the diabetic populations (Bruno and Landi 2011). The USA and Mexico are the most affected countries, showing the highest prevalence (with 10.3% and 10.8%, respectively) (Shaw et al. 2010), not only in the older population, but with an increasing incidence also in children, especially 6–11 years old age group (Ogden et al. 2010).

Gathering WHO's general scheme for the diagnosis of DM (WHO 1985), type 1 diabetes mellitus (T1DM) is referred to as beta-cell destruction, usually leading to absolute insulin deficiency, presenting in two forms: autoimmune and idiopathic. T2DM is an acquired form of diabetes and it may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with or without insulin resistance. This form of diabetes is frequently undiagnosed for many years because the hyperglycaemia is often not severe enough to provoke noticeable symptoms of diabetes. Other classes included in that classification were impaired glucose

Correspondence: Simonetta Ballali, PROCHILD Onlus, Piazza San Giovanni 2, Trieste (TS), Italy. Tel: + 39 040 662500. Fax: + 39 0498251143. E-mail: simonetta.ballali@prochild.eu

ISSN 0963-7486 print/ISSN 1465-3478 online
DOI: 10.3109/09637486.2011.637487

tolerance (IGT) as well as gestational diabetes mellitus. Both IGT and impaired fasting glucose (IFG) are included in the term prediabetes. People with prediabetes have higher than normal blood glucose levels, but they are not elevated enough to be diagnosed as diabetes.

Until recently, diabetes in children was virtually synonymous with T1DM, whereas T2DM was a disease of middle aged and the elderly. Over the past 10–20 years, an alarming increase in the prevalence of T2DM has been reported from paediatric diabetes centres in North America and elsewhere in the world (Botero and Wolfsdorf 2005). Prevention of T2DM should begin before or during the IFG and/or IGT stage.

In this background, functional foods (FFs), with their specific health effects, represent a new mode of thinking about the relationships between food and health in everyday life.

The definition of FFs still lingers in a wide range of possibilities, laying its meaning essentially as a marketing term and globally it is not recognized by law (Henry 2010). Among different definitions, the European Commission's Concerted Action on Functional Food Science in Europe, coordinated by International Life Science Institute, Europe, defined FF as a food product that together with the basic nutritional impact has beneficial effects on one or more functions of the human organism, thus either improving the general and physical conditions or/and decreasing the risk of the evolution of diseases (ILSI 1999). The amount of intake and form of the FF should be as it is normally expected for dietary purposes, not taken in the form of pill or capsule.

Consumers do not perceive FFs as medicines, but since they are interested in health-related issues they are more prone to consume these products, recognizing them as bearing healthier values than the conventional products (Sabbe et al. 2009). In the last decades consumer demands in the field of food production have changed considerably. Consumers more and more believe that foods contribute directly to their health (Mollet and Rowland 2002). Today, foods are not intended to only satisfy hunger and to provide necessary nutrients for humans but also to prevent nutrition-related diseases and improve physical and mental well-being of the consumers (Roberfroid 2000). In this regard, FFs play an outstanding role. The growing demand on such foods can be explained by augmented costs of healthcare, steady enlarged life expectancy and desire for an improved quality life through all life stages.

Considering actual policies implemented in order to stop the epidemic of diabetes, they have increasingly focused on targeting risk factors present in youth. At present, two main streams have been identified as promising strategies: school-based interventions, such as the HEALTHY study (Hirst et al. 2009) where the reduction in glucose levels and other risk factors have been obtained integrating nutritional changes, physical activity, behavioural, social-marketing components and external policies focused on culturally embedded risk factors (such as sugar-sweetened beverages, calorically dense foods, excessive television and video watching, high price and limited availability of healthy foods and community designs that discourage physical activity) (Ebbeling et al. 2002). In the first case, transformations are requested in a broader form, touching not only the behavioural field, but also involving all other aspects related to the child's life, such as psychology, cognition, physical activity and family background. In the second case, focusing on single factors translates into a crescent number of banning policies, targeting those elements related to an increased energy intake such as snacks in schools, commercials aimed at children, high density energy food and beverages, at the same time raising doubts on how these measures potentially disregard the complexity of responsibilities regarding overweight, infringing upon personal freedom regarding lifestyle choices, raising children, private enterprises' actions or policy's choices by schools and other organizations (Ten Have et al. 2011).

To tackle diabetes epidemic, taking into account also the costs that the public health sector is facing, preventive strategies need to consider the complexity of diseases development, improving access and knowledge towards natural way of prevention and management for the affected ones, properly intervening in both health claimed food support and promotion and consumers' education. Although many functional ingredients are nowadays emerging for their potential in diseases prevention in public health and industry sectors, they have been widely known and used as traditional medicine components for centuries. The aim of this paper was to analyse the potential role that functional ingredients might play in the prevention of diabetes, considering different molecules that have shown promising results. These ingredients have moreover a beneficial effect in the management of diabetes, showing their broad potential in terms of cost-effective public health policies.

Functional ingredients in diabetes prevention and management

There are three key defects in the onset of hyperglycaemia in DM, namely increased hepatic glucose production, diminished insulin secretion and impaired insulin action (Chiasson and Rabasa-Lhoret 2004). FFs act comprehensively increasing insulin secretion, enhancing glucose uptake by adipose and skeletal muscle tissues and inhibiting intestinal glucose absorption and hepatic glucose production. Hereafter, the potential of functional ingredients will be considered in animal and human models, presenting the different mechanisms of action of the single elements. All data are resumed in Table I.

Stevioside

A natural sweetener has widely caught attention, due not only to its properties of sucrose's substitute, but also for its potential functional properties. Stevioside is a sweet glycoside extracted from *Stevia rebaudiana* Bertoni, a small shrub originally grown in South America, particularly in Brazil and Paraguay where it is known as Stevia or honey leaf, Kaa-he-e (Hanson and De Oliveira 1993). Extracts are being used commercially in many countries for sweetening a variety of products including pickled vegetables, sea foods, soft drinks, soy sauce and confectionary products. Stevioside is an intense sweetener and the extract of its source finds extensive use in countries such as Japan, China, Russia, Korea, Paraguay, Argentina, Indonesia, Malaysia, Australia, New Zealand, South America and others, to sweeten local teas, medicines, food and beverages (Kinghorn and Soejarto 2002). Oral stevioside is taken up by the human body at extremely low levels (Geuns et al. 2003; Geuns 2003) and none of the digestive enzymes from the gastro-intestinal tract of different animals and human body are able to degrade stevioside into steviol. In one experiment, the bacteria from the human colon were also found to form steviol epoxide *in vitro*, which was again metabolized to steviol (Hutapea et al. 1997). Renwick (2008) reviewed the literature on the metabolism of stevioside and rebaudioside A by intestinal microbiota; steviol was reported to be the only metabolite in faeces which is not further metabolized, thereby playing the role of low calorie sweetener. The use of stevioside as a functional ingredient has been addressed due to its biological effects and therefore to its potential applications. *In vitro* studies with incubated mouse pancreatic islets have indicated that hypoglycaemic effects of stevioside and steviol result from the stimulation of insulin secretion via the direct action of these compounds on β-cells and the β-cell line INS-1 (Jeppesen et al. 2000). In a recent study, results from Gregersen et al. (2004) showed a positive association between reduced postprandial blood glucose (PPG) response compared to placebo, in T2DM patients, questioning whether significant results can be obtained only in high glycaemic level subjects. Thomas (2010) has widely discussed the use of stevioside in different conditions of body weight (BW), T2DM and MS, stressing the deep need of experimental studies on humans in order to confirm the results seen in animals, primarily in rats, but highlighting the various utilities and potential benefits seen with stevioside.

Several studies on animals and humans have been performed in order to assess the potential toxicology of this compound. Taken together, most studies are in agreement demonstrating that oral stevioside, at an acceptable daily intake (5 mg/kg BW), is safe and not carcinogenic or teratogenic (Chatsudthipong and Muanprasat 2009). An ADI of 0–2 mg/kg of BW for steviol, equivalent to 0–5 mg/kg BW of stevioside, as suggested by Joint FAO/WHO Expert Committee on Food Additives (JECFA 2006), was estimated to yield a stevioside concentration in colon at about 0.05–0.2 mM, a concentration at which no toxicity to intestinal cells is expected (Boonkaewwan et al. 2008). A recent study showed that after maximum oral administration of single dose of 4.2 mg of stevioside/kg BW in humans, the highest mean concentration in plasma of steviol glucuronide and free steviol in plasma was 1.89 μg/ml (3.7 μM) and 0.19 μg/ml (0.38 μM), respectively (Wheeler et al. 2008), stressing how these levels are not toxic on human cell and how steviol does not undergo any conversion in the process (Wheeler et al. 2008).

Cinnamon

Another FF that has been evaluated in depth as effective on DM is cinnamon. Extensive literature has shown that cinnamon may exert beneficial effects on many of the factors associated with MS, including insulin sensitivity, glucose, lipids, antioxidants, inflammation, blood pressure and BW (Qin et al. 2010). Poor insulin sensitivity is a precursor to T2DM and is often characterized by high fasting blood glucose (FBG), defined as blood glucose levels of 5.5–6.9 mmol/l (Grant et al. 2009).

First *in vitro* evidence for insulin-enhancing activity by cinnamon was reported by Anderson group in 1990 (Khan et al. 1990), who further characterized the active compounds as water soluble polyphenols (Anderson et al. 2004). Imparl-Radosevich et al. (1998) performed enzyme studies *in vitro*, showing that cinnamon bioactive compounds can stimulate autophosphorylation of a truncated form of the insulin receptor and can inhibit PTP-1, a rat homologue of a tyrosine phosphatase that in turn dephosphorylates the insulin receptor-beta subunit, decreasing therefore their sensitivity to insulin. Also in human studies, reduced phosphorylation of the insulin receptors was found in subjects with T2DM (Cusi et al. 2000).

Mouse 3T3-L1 adipocytes cell cultures have also been used by Cao et al. (2007) as a model system in the studies of the mechanisms of cinnamon polyphenols in insulin signal transduction pathway (see Figure 1). Recently, Couturier et al. (2011) reported that addition of cinnamon to a diet-induced model of insulin resistant rat reversed insulin resistance and enhanced liver glycogen in association with the regulation of the expression of multiple genes and proteins involved in insulin sensitivity and glycogen metabolism, even though there were no significant changes in the animals consuming the control diet plus cinnamon.

After a study by Khan and colleagues (2003) reporting statistically and clinically significant effects of cinnamon on glucose and lipid metabolism of T2DM-affected people, several clinical trials were

Table I. Overview of promising FF in diabetes prevention and management.

	Animal studies		Human studies				
Functional ingredient	Reference	Possible action	Reference	Sample	Possible action	Effect	Toxicity
Stevioside	Jeppesen et al. (2000)	Stimulation of insulin secretion via direct action on β-cells and the β-cell line INS-1	Gregersen et al. (2004)	T2DM subjects; healthy subjects		Reduced postprandial blood glucose	Oral stevioside, at an acceptable daily intake (5 mg/kg BW), is safe and not carcinogenic or teratogenic
Cinnamon	Jeppesen et al. (2000)	Autophosphorylation of a truncated form of the insulin receptor and inhibition of PTP-1; reversing insulin resistance and enhancing liver glycogen in association with the regulation of the expression of multiple genes and proteins involved in insulin sensitivity and glycogen metabolism	Cusi et al. (2000), Khan et al. (2003), Cao et al. (2007), Hlebowicz et al. (2007), Qin et al. (2010)	T2DM subjects; healthy subjects	Reduced phosphorylation of the insulin receptors; delaying gastric emptying	Reduced postprandial blood glucose	Potential effetcs may be overcome using aqueous extracts of cinnamon
Fenugreek	Sharma et al. (1990), Raju et al. (2001)	Altered glycolytic, gluconeogenic and lipogenic enzymes activity	Yeh et al. (2003), Srinivasan (2005)	T2DM subjects; healthy subjects	Delay of gastric emptying and suppressing release of gastric inhibitory peptides and insulinotropic hormones	Reduced fasting blood sugar and improved glucose tolerance test	Lack of toxic effect at proposed used levels
Allium species	Roman-Ramos et al. (1995), El-Demerdash et al. (2005)	Inhibited the formation of advanced glycation end products	Tjokroprawiro et al. (1983), Kiesewetter et al. (1991)	Healthy subjects	Stimulation of insulin secretion by pancreas and by complexing with endogenous thiol-containing molecules, to prevent sulphydryl inactivation of insulin	Decrease in fasting serum glucose	No toxicity found
Gymnema sylvestre	Shanmugasundaram et al. (1990a)	Possible regeneration of the islets of Langerhans	Khare et al. (1983), Okabayashi et al. (1990)	T1DM and T2DM insulin-dependent subjects; healthy subjects	Insulin secretagogue	Inhibition of glucose uptake in the intestine	No toxicity found
Mormodica charantia (Bitter Melon)	Karunanayake et al. (1984)	Activation of PPARa, activation of AMP-activated protein kinase (*in vitro* tests)	Chuang et al. (2006), Cheng et al. (2008)	T1DM and T2DM subjects	Insulin secretion, tissue glucose uptake, liver muscle glycogen synthesis, glucose oxidation and decreased hepatic gluconeogenesis		No toxicity found
Ginseng	Waki et al. (1982), Suzuki et al. (1991), Ohnishi et al. (1996), Yuan et al. (1998)	Gastric-modulating effects; enhances glucose liver absorption and insulin biosynthesis	Vuksan and Sievenpiper (2005), Sievenpiper et al. (2006)	T2DM; non-diabetic patients; pre-diabetic patients	Decrease in FBG and HbA1c, glycaemic response to OGTT, plasma fasting insulin		Potential side effects include nervousness, excitation, headache, hypertension, insomnia

performed in order to evaluate cinnamon's ability to prevent T2DM or reduce risk factors associated with it (Qin et al. 2010). Whole cinnamon or water soluble extracts were tested on healthy human subjects with a mean lean body mass lower than 25, subjects with MS, T2DM patients and woman with polycystic ovary syndrome. During an 8-week treatment period, oral ingestion of a commercial cinnamon extract (Cinnulin PF) 1 gg/day resulted in a significant reduction in FBG, as well as in insulin resistance.

In a study involving 14 healthy subjects, the addition of 6 g of cinnamon to rice pudding significantly delayed gastric emptying and lowered PPG (Hlebowicz et al. 2007). Given that 6 g of cinnamon is not a quantity ordinarily used in food, the experiment was repeated using 1 and 3 g portions (Hlebowicz et al. 2009), but no significant effects on gastric-emptying rate, satiety, glucose, glucose-dependent insulinotropic polypeptide or ghrelin response were observed. However, ingestion of 3 g cinnamon reduced postprandial serum insulin and increased GLP-1 concentrations indicating a relationship between the amount of cinnamon consumed and the decrease in insulin concentration.

Many clinical trials with modest sample populations have investigated the effects of cinnamon on FPG levels, producing contrasting results (Kirkham et al. 2009). In a recent work by Davis and Yokoyama (2011), a meta-analysis was performed using a random-effects model on eight chosen studies. The results showed that the intake of cinnamon/cinnamon extracts by T2DM subjects or prediabetics does lower their blood glucose significantly albeit modestly, with percentage declines in FBG, of the same order of magnitude as for metformin (an oral drug used for T2DM treatment). The results obtained in this work are in contrast to the previous two meta-analyses (Baker et al. 2008; Kirkham et al. 2009). The authors suggested that the reason behind the difference in outcome may be due to the inclusion of the more recent reports and/or larger study populations.

Several articles that will be not regarded in depth in this review suggest that cinnamon-derived active compounds may not only improve the function of insulin but also act as antioxidants and exert anti-inflammatory activity. Cinnamon extracts have been shown *in vitro* to enhance mRNA levels of anti inflammatory Tristetraprolin (TTP) protein (Baker et al. 2008), and a commercial preparation of cinnamon water extracts tested on TNF-treated hamsters intestine cells resulted in the improvement of inflammation-related intestinal dyslipidaemia (Qin et al. 2009). Cinnamon bark showed significant inhibitory effects on the formation of advanced glycation end products (AGEs), whose accumulation *in vivo* has been implicated as a major pathogenic process in diabetic complications. The inhibitory effect was mainly attributed to the anti-glycation

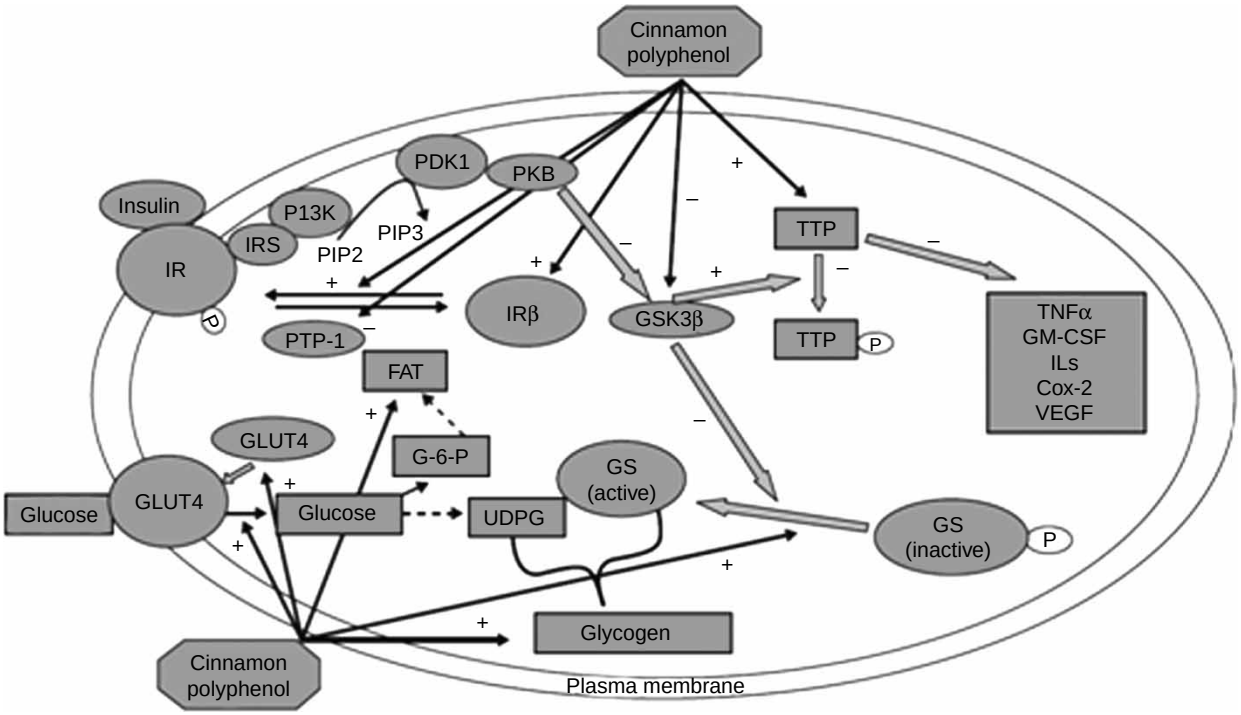

Figure 1. (1) Cinnamon polyphenol (CP) activates insulin receptors by increasing their tyrosine phosphorylation and by decreasing phosphatase activity that inactivates the receptor; (2) CP increases the amount of insulin receptor-β and GLUT4 proteins; (3) CP increases glycogen synthase activity and glycogen accumulation; (4) CP decreases glycogen synthetase kinase-3β (GSK3β) activity; (5) CP increases the amount of tristetraprolin (TTP) protein and (6) CP may increase the activity of TTP by decreasing its phosphorylation through the inhibition of GSK3β activity (Pasupuleti and Anderson 2008).

activities of some of its phenolic components such as trapping reactive carbonyl species (Peng et al. 2008).

Long-term effects of cinnamon consumption have yet to be studied but its widespread use as a spice would suggest that it is unlikely that a moderate intake could lead to harmful effects. On the other hand, concerns about high doses of whole cinnamon have been raised, regarding essentially the spice content in coumarin and cinnamaldehyde (Lungarini et al. 2008). However, since aqueous extracts of cinnamon (in which many of the organic components are removed when cinnamon oil is extracted, including cinnamaldehyde and fat-soluble coumarin) have basically the same *in vitro* insulin-potentiating activity as extracts from the cinnamon before the oil is removed (Pasupuleti and Anderson 2008), supplementation with soluble cinnamon extracts should overcome this problem.

Fenugreek

The anti-diabetic efficacy of *Trigonella foenum graecum* (Fenugreek) has been tested in several preliminary human trials, wherein whole seeds, seeds extracts and leaves were screened for activity. Although leaves did not show any beneficial hypoglycaemic effect (Khan et al. 1995), it is believed that dietary fibres in the seeds may act in delaying gastric emptying and suppressing release of gastric inhibitory peptides and insulinotropic hormones (Srinivasan 2005). Fenugreek was also found to act on the metabolic clearance rate of glucose and erythrocyte insulin receptors, as reported by a study carried out on a T2DM patient who was given 25 g fenugreek seeds for 15 days (Sharma et al. 1990). In a trial aimed at elucidating the therapeutic role of fenugreek on alloxan-induced diabetic rats, oral administration of whole seed powder (5% in the diet for 21 days) improved glucose homeostasis as a result from altered glycolytic, gluconeogenic and lipogenic enzymes activity, whose levels were restored to control values (Raju et al. 2001).

A recent meta-analysis on the effects of traditional herbal medicines on T2DM patients (Suksomboon et al. 2011), performed on randomized placebo-controlled trial of at least 8 weeks duration, highlighted that fenugreek supplementation can significantly improve glycated haemoglobin (HbA1c) levels.

Also T1DM patient's condition was shown to benefit from fenugreek supplementation; in a long-term trial isocaloric diets were supplemented randomly to patients for 10 days with and without 100 g/day of fenugreek powder divided into two equal doses. The fenugreek diet significantly reduced FBG and improved the glucose tolerance test (Sharma et al. 1990).

Even though further clinical studies are needed to confirm the therapeutic power of this herb, preliminary evidence and substantial lack of toxic effects at proposed use levels (Yeh et al. 2003) make Fenugreek a promising candidate as a FF for diabetes management.

Allium *species*

Several studies on healthy and diabetic animals reported evidence of positive regulation of blood glucose and insulin levels by garlic and onion (Roman-Ramos et al. 1995; El-Demerdash et al. 2005). The active principles of the bulbs were identified as sulphur compounds, S-allyl cysteine sulphoxide in garlic and SMCS in onion, which were reported to possess as much as 60–90% hypoglycaemic potency of tolbutamide (a drug used in the management of T2DM) (Jain and Vyas 1975).

It is believed that the active principles act by stimulating insulin secretion by pancreas and by complexing with endogenous thiol-containing molecules to prevent sulphydryl inactivation of insulin (Augusti 1975).

In vitro studies also showed that either aged garlic extracts and S-allyl cysteine inhibited the formation of AGEs that are commonly associated with hyperglycaemia and complications of diabetes (Ahmad et al. 2007).

In recent meta-analyses by Kook et al. (2009), a systematic literature search was conducted to evaluate the effects of extracts or single components of garlic and onion on several effect factors in induced diabetic rats, such as BW, blood glucose, plasma cholesterol, triglycerides, HDL and liver glycogen concentration. The results suggested that only onion extracts or its single components may exert anti-diabetic effects by lowering blood glucose and BW, while garlic was not significantly effective.

Only a limited number of clinical studies focused on garlic are available and results are quite contradictory. One high-quality randomized control trial (RCT) on *Allium sativum* in humans was designed to examine thrombocyte aggregation in non-diabetic individuals. The administration of 800 mg of garlic powder over a period of 4 weeks resulted, however, in a decrease in fasting serum glucose (Kiesewetter et al. 1991). Two available clinical studies on the supplementation of garlic in T2DM patients (Sitprija et al. 1987) did not show consistent glucose or insulin responses after garlic supplementation, while Ashraf et al. (2011) found that addition of garlic tablets to anti-diabetic agent metformin was effective in controlling FBG levels.

A. cepa or its isolated active principles were tested on both T2DM and normal subjects, resulting in a significant fall in the blood glucose level and rise in the serum insulin (Augusti and Benaim 1975; Tjokroprawiro et al. 1983).

Gymnema sylvestre

The active constituents of *G. sylvestre* were isolated from the saponin fraction of leaves extract and identified as gymnemosides and gymnemic acids

(Murakami et al. 1996; Yoshikawa et al. 1997). Besides the anti-diabetic and anti-inflammatory properties attributed to this plant by traditional Indian medicine, *Gymnema* leaves are also known to alter taste modulation in humans, particularly suppressing sweet taste sensations.

Animal and *in vitro* studies revealed that *G. sylvestre* may control glucose homeostasis in insulin-dependent diabetes mellitus (IDDM), mainly acting as insulin secretagogue. Shanmugasundram et al. (1990a) observed that FBG levels of streptozoticin-treated rats returned to control level after 20 and 60 days of oral administration of soluble extracts of the plant, suggesting a possible regeneration of the islets of Langerhans by *G. sylvestre*. Later, Persaud and colleagues demonstrated that the soluble *G. sylvestre* extracts stimulate insulin release by increasing the membrane stability of pancreatic β-cell lines, rather than by stimulating exocytosis (Shimizu et al. 1997).

The beneficial effects of *Gymnema* extracts supplementation to animal model of T2DM were in part confirmed in humans by Shanmugasundaram et al. (1990b); 400 mg/day of GS4 extract administered to IDDM patients resulted in lower FBG, HbA1c and glycosylated plasma protein levels, allowing for reduction in insulin requirements.

Two clinical trials to test the effectiveness of *G. sylvestre* on T2DM reported promising results. Aqueous extracts of the plant (3 × 2 g) given to patients for 15 days significantly reduced FBG values and improved the tolerance to an oral glucose load (Khare et al. 1983). GS extracts administration were also found to be effective in controlling hyperglycaemia as a supplement to other conventional oral hypoglycaemic drugs (Baskaran et al. 1990). The only data available on *Gymnema* effects on non-diabetic subjects were published by Okabayahi et al. (1990); administration of 1 g/kg BW of GS4 extract to 18-h fasted rats significantly attenuated the serum glucose response to oral administration of 1 g/kg glucose.

Other proposed mechanisms for glucose homeostasis maintenance by *G. sylvestre* relate to the inhibition of glucose uptake in the intestine (Shimizu et al. 1997) and regulation of enzymes related to the utilization of glucose (Shanmugasundaram et al. 1983).

Mormodica charantia *(Bitter Melon)*

The positive influence of *M. charantia* in diabetic animal models has been reviewed in many scientific works (Uebanso et al. 2007). Active components were found in the extracts of fruit pulps, seeds and whole plant and identified as charantin, vicine and polypeptide-p (an insulin-like protein similar to bovine insulin). The proposed mechanisms of action include insulin secretion, tissue glucose uptake, liver muscle glycogen synthesis, glucose oxidation and decreased hepatic gluconeogenesis (Yeh et al. 2003). Cell-based assays (Chuang et al. 2006; Cheng et al. 2008) revealed that AMP-activated protein kinase and PPARs transcription factors (both involved in the homeostasis of glucose) may be the target of active components isolated from *M. charantia*. Bitter melon showed dose-related hypoglycaemic effects on trials involving diabetic animal models (see Pasupuleti & Anderson, Nutraceuticals, Glycemic Health & Type 2 Diabetes). Karunanayake et al. (1984) reported on laboratory animals that improvement in glucose tolerance was best with fresh juice, with decreasing activity upon storage.

Hypoglycaemic effects of the herb were also investigated in non-diabetic animals. Chronic administration of Cerasee (a variety of *M. charantia*) for 13 days improved glucose tolerance in normal mice, without significantly altering plasma insulin concentration (Bailey et al. 1985). In a study involving glucose-fed normal rats, a significant hypoglycaemic effect was observed when pulp juice was fed 45 min before the oral glucose load (Ali et al. 1993).

As reported by recent reviews by Leung et al. (2009) and Ooi et al. (2010), clinical studies regarding hypoglycaemic effect of bitter melon are sparse and low in quality design, leading often to contradictory results and insufficient evidence. The different forms of administration used in the tests (dried powder, fresh fruit and solvent extracts) and the outcome measures taken into consideration differ widely, making it impossible to analyse the data using meta-analysis (Leung et al. 2009).

However, as no or limited adverse effect was reported on such trials, further better designed studies with sufficient sample size and statistical power are needed to shed more light on the therapeutic potential of *M. charantia* that remains one of the most promising candidate between FFs for diabetic patients.

Panax *genus*

The *Panax* genus belonging to the *Araliaceae* family includes several different types of ginseng plant but most reports investigated the hypoglycaemic potential of the plant on Asian (*Panax*) or American (*Panax quinquefolius L.*) ginseng.

Most of the pharmacological actions of ginseng are attributed to its saponins, referred to as ginsenosides (Attele et al. 2002).

Ginsenosides profiles can be used to discriminate between ginseng plants, as different species differ in content type and ratios of these molecules (Attele et al. 2002).

Experiments on animals have indicated several possible mechanisms by which this plant may control blood glucose levels. American ginseng showed strong gastric-modulating effect on brain neuronal activity (Yuan et al. 1998) and Suzuki et al. (1991) observed inhibition of gastric secretion by Asian ginseng, thus suggesting that ginseng may slow the digestion of food,

decreasing the rate of carbohydrate absorption into portal hepatic circulation.

After oral administration of water extract of ginseng radix (GR) to normal and epinephrine-induced hyperglycaemic mice, a significant decrease in the blood glucose level 4 h after its administration was observed along with an increased GLUT2 transporter content in the liver. These results suggest that the hypoglycaemic activity of GR is presumably due, at least in part, to the increment of GLUT2 protein content (Ohnishi et al. 1996). DPG-3-2, a component of GR, was shown to stimulate insulin biosynthesis in different preparations of pancreas from hyperglycaemic animals (Ohnishi et al. 1996).

Most of the available clinical trials adopting standardized batch of ginseng preparations utilized American and Korean ginseng.

Vuskan and Sievenpiper (2005) performed several short and long-term clinical studies to test ginseng's ability to produce reproducible and sustainable glycaemic reduction. In the first two acute 'Phase I RCTs', they noted that doses from 1 to 9 g were equally efficacious in decreasing the glycaemic response to 25 g oral glucose tolerance test (OGTT) in both normoglycaemic and T2DM subjects. Doses from 1 to 9 g were equally efficacious and a time-related effect of administration was observed only in normoglycaemic subjects (the glycaemic response was reduced only if ginseng was given at least 40 min before the test).

A second series of controlled crossover trials was designed to monitor the effect of ginseng supplementation over an 8-week period. One gram of the same ginseng extract used in 'phase I' experiments was administered 40 min preprandially thrice daily in 24 subjects with T2DM. The result was a significant decrease in FBG and HbA1c values compared with the placebo.

The same experimental strategy was also used to design and test a new efficacious ginseng preparation and relative modality of administration (Red Korean Ginseng rootless) (Sievenpiper et al. 2006).

In a recent work published by Reeds et al. (2011), overweight to obese subjects with IGT or newly diagnosed T2DM were randomized to 30 days of treatment with ginseng (a), ginsenoside (b) or placebo. The authors found that (a) and (b) did not improve β-cell function (measured as the disposition index) nor insulin sensitivity, proposing poor ginseng systemic bioavailability as the reason for the absence of a therapeutic effect. Precedents findings by Vuskan and Sievenpiper (2005) and Sievenpiper et al. (2006) were questioned for large drop-out rate and concomitant weight loss of the subjects during the study that could have confounded the interpretations of the results. Further studies are needed to shed light on the therapeutic potential of ginseng, taking into considerations that variations in response may reflect chemical heterogeneity of different ginseng batches.

A natural way for the development of effective preventive strategies

Possibilities given from the novel distribution of FFs for DM's prevention need to be assessed in order to allow a different approach to the epidemic. Similar to pharmaceutical agents, FFs possess physiological and molecular targets that modulate clinical end points associated with chronic disease (Marinangeli and Jones 2010). Using the same research strategies utilized in drugs and integrators' developments appears to be a reducing factor for this new approach's diffusion. Food & Health Forum at the Royal Society of Medicine (Mitchell et al. 2010) suggested that an alternative approach would be to look at the probability of association between a food and an effect rather than looking for conclusive proof of cause and effect.

Preventive policies have to be supported by strong evidence-based data that, when considering FF though the pharmacological point of view, seem to be lacking.

As seen in the previous section, functional ingredients such as bitter melon had a large use as dietary supplements and ethnomedicine throughout centuries for relieving symptoms and conditions related to diabetes. Sound data come from biochemical and animal studies, but clinical trial often presents small sample size, lack of control and poor study designs (Leung et al. 2009).

For diseases developed over a long period of time, it may not be possible to perform a study for a long enough period to see a statistically significant difference in the incidence of disease between study subjects in the treatment and the control groups (Rasnake et al. 2008). The need of validated surrogate end points is linked to the possibility to evaluate the effect of FFs in prevention of chronic diseases such as DM.

The National Institutes of Health and FDA's Center for Drug Evaluation and Research have identified surrogate endpoints for risk of T2DM, blood glucose concentration (FPG and oral glucose tolerance) and insulin resistance (FDA 1999; Trumbo and Ellwood 2006).

Other well-known surrogate end points used in DM studies include glycated haemoglobin (HbA1c) and PPG. Nevertheless, it must be stressed that clinical trials convincingly demonstrating a direct relationship between reduction in PPG and improvement in patient-important end points are not yet available.

New strategies involving the use of FF should be validated through large-scale population trials, specifically on T2DM prevention, that is twinning the worldwide effort in obesity prevention. All the surrogate end points presented in the present paper have shown a large potential in reducing PPG, increasing insulin secretion, enhancing glucose uptake

by adipose and skeletal muscle tissues, inhibiting intestinal glucose absorption and inhibiting hepatic glucose production. The identification of common guidelines to implement the development of health claims related to FF could therefore reduce the gap between market and consumers, thereby implementing preventive policies within a common framework.

FFs represent a valid alternative in consumers' choices, ensuring biological properties that contribute to a healthier nutrition. The conflicting conclusions so far obtained may be a result of the differences in the type of subject, the methods of evaluating, the definition of the end points and of small samples' analysis. Increased knowledge on FFs actions on humans and development of large population studies are the necessary steps that need to be taken into account in future public health agenda. These advances will create the possibility of not only identifying the precise functional aspects of the single components, but moreover to offer sustained evidence-based strategies for diabetes' prevention and management at population level.

Acknowledgements

The authors would like to thank Prof. Luigi Bubacco for his valuable comments and suggestions, and Prof. Dario Gregori and Prof. George Halpern for the opportunity given to present this work. FRI, Food Research and Innovation is a spin off co-participated by the University of Padova, Italy.

Declaration of interest: The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

References

Ahmad MS, Pischetsrieder M, Ahmed N. 2007. Aged garlic extract and S-allyl cysteine prevent formation of advanced glycation endproducts. Eur J Pharmacol 561:32–38.

Ali L, Khan AK, Mamun MI, Mosihuzzaman M, Nahar N, Nur-e-Alam M, Rokeya B. 1993. Studies on hypoglycemic effects of fruit pulp, seed, and whole plant of *Momordica charantia* on normal and diabetic model rats. Planta Med 59:408–412.

Anderson RA, Broadhurst CL, Polansky MM, Schmidt WF, Khan A, Flanagan VP, et al. 2004. Isolation and characterization of polyphenol type-A polymers from cinnamon with insulin-like biological activity. J Agric Food Chem 52:65–70.

Ashraf R, Khan RA, Ashraf I. 2011. Garlic (*Allium sativum*) supplementation with standard antidiabetic agent provides better diabetic control in type 2 diabetes patients. Pak J Pharm Sci 24: 565–570.

Attele AS, Zhou YP, Xie JT, Wu JA, Zhang L, Dey L, et al. 2002. Antidiabetic effects of *Panax* ginseng berry extract and the identification of an effective component. Diabetes 51: 1851–1858.

Augusti KT. 1975. Studies on the effect of allicin (diallyl disulphide-oxide) on alloxan diabetes. Experientia 31:1263–1265.

Augusti KT, Benaim ME. 1975. Effect of essential oil of onion (allyl propyl disulphide) on blood glucose, free fatty acid and insulin levels of normal subjects. Clin Chim Acta 60:121–123.

Bailey CJ, Day C, Turner SL, Leatherdale BA. 1985. Cerasee, a traditional treatment for diabetes: studies in normal and streptozotocin diabetic mice. Diabetes Res 2:81–84.

Baker WL, Gutierrez-Williams G, White CM, Kluger J, Coleman CI. 2008. Effect of cinnamon on glucose control and lipid parameters. Diabetes Care 31:41–43.

Baskaran K, Kizar Ahamath B, Radha Shanmugasundaram K, Shanmugasundaram ER. 1990. Antidiabetic effect of a leaf extract from *Gymnema sylvestre* in non-insulin-dependent diabetes mellitus patients. J Ethnopharmacol 30:295–300.

Boonkaewwan C, Ao M, Toskulkao C, Rao MC. 2008. Specific immunomodulatory and secretory activities of stevioside and steviol in intestinal cells. J Agric Food Chem 56:3777–3784.

Botero D, Wolfsdorf JI. 2005. Diabetes mellitus in children and adolescents. Arch Med Res 36:281–290.

Bruno G, Landi A. 2011. Epidemiology and costs of diabetes. Transplant Proc 43:327–329.

Cao H, Polansky MM, Anderson RA. 2007. Cinnamon extract and polyphenols affect the expression of tristetraprolin, insulin receptor, and glucose transporter 4 in mouse 3T3-L1 adipocytes. Arch Biochem Biophys 459:214–222.

Chatsudthipong V, Muanprasat C. 2009. Stevioside and related compounds: therapeutic benefits beyond sweetness. Pharmacol Ther 121:41–54.

Cheng HL, Huang HK, Chang CI, Tsai CP, Chou CH. 2008. A cell-based screening identifies compounds from the stem of *Momordica charantia* that overcome insulin resistance and activate AMP-activated protein kinase. J Agric Food Chem 56: 6835–6843.

Chiasson JL, Rabasa-Lhoret R. 2004. Prevention of type 2 diabetes: insulin resistance and beta-cell function. Diabetes 53(Suppl 3): S34–S38.

Chuang CY, Hsu C, Chao CY, Wein YS, Kuo YH, Huang CJ. 2006. Fractionation and identification of 9c, 11t, 13t-conjugated linolenic acid as an activator of PPARalpha in bitter gourd (*Momordica charantia* L.). J Biomed Sci 13:763–772.

Couturier K, Qin B, Batandier C, Awada M, Hininger-Favier I, Canini F, et al. 2011. Cinnamon increases liver glycogen in an animal model of insulin resistance. Metabolism 60:1590–1597.

Cusi K, Maezono K, Osman A, Pendergrass M, Patti ME, Pratipanawatr T, et al. 2000. Insulin resistance differentially affects the PI 3-kinase- and MAP kinase-mediated signaling in human muscle. J Clin Invest 105:311–320.

Davis PA, Yokoyama W. 2011. Cinnamon intake lowers fasting blood glucose: meta-analysis. J Med Food 14:884–889.

Ebbeling CB, Pawlak DB, Ludwig DS. 2002. Childhood obesity: public-health crisis, common sense cure. Lancet 360:473–482.

El-Demerdash FM, Yousef MI, El-Naga NI. 2005. Biochemical study on the hypoglycemic effects of onion and garlic in alloxan-induced diabetic rats. Food Chem Toxicol 43:57–63.

FDA 1999. Guidance for industry significant scientific agreement in the review of health claims for conventional foods and dietary supplements. Washington, DC. Center for food safety and applied nutrition, office of special nutritionals.

Geuns JM. 2003. Stevioside. Phytochemistry 64:913–921.

Geuns JM, Augustijns P, Mols R, Buyse JG, Driessen B. 2003. Metabolism of stevioside in pigs and intestinal absorption characteristics of stevioside, rebaudioside A and steviol. Food Chem Toxicol 41:1599–1607.

Grant SJ, Bensoussan A, Chang D, Kiat H, Klupp NL, Liu JP, Li X. 2009. Chinese herbal medicines for people with impaired glucose tolerance or impaired fasting blood glucose. Cochrane Database Syst Rev, CD006690.

Gregersen S, Jeppesen PB, Holst JJ, Hermansen K. 2004. Antihyperglycemic effects of stevioside in type 2 diabetic subjects. Metabolism 53:73–76.

Hanson JR, De Oliveira BH. 1993. Stevioside and related sweet diterpenoid glycosides. Nat Prod Rep 10:301–309.

Henry CJ. 2010. Functional foods. Eur J Clin Nutr 64:657–659.

Hirst K, Baranowski T, DeBar L, Foster GD, Kaufman F, Kennel P, et al. 2009. HEALTHY study rationale, design and methods: moderating risk of type 2 diabetes in multi-ethnic middle school students. Int J Obes (Lond) 33(Suppl 4):S4–20.

Hlebowicz J, Darwiche G, Bjorgell O, Almer LO. 2007. Effect of cinnamon on postprandial blood glucose, gastric emptying, and satiety in healthy subjects. Am J Clin Nutr 85:1552–1556.

Hlebowicz J, Hlebowicz A, Lindstedt S, Bjorgell O, Hoglund P, Holst JJ, et al. 2009. Effects of 1 and 3 g cinnamon on gastric emptying, satiety, and postprandial blood glucose, insulin, glucose-dependent insulinotropic polypeptide, glucagon-like peptide 1, and ghrelin concentrations in healthy subjects. Am J Clin Nutr 89:815–821.

Hutapea AM, Toskulkao C, Buddhasukh D, Wilairat P, Glinsukon T. 1997. Digestion of stevioside, a natural sweetener, by various digestive enzymes. J Clin Biochem Nutr 23:177–186.

ILSI 1999. Scientific concepts of functional foods in Europe: consensus document. Br J Nutr 81(Suppl 1):S1–27.

Imparl-Radosevich J, Deas S, Polansky MM, Baedke DA, Ingebritsen TS, Anderson RA, Graves DJ. 1998. Regulation of PTP-1 and insulin receptor kinase by fractions from cinnamon: implications for cinnamon regulation of insulin signalling. Horm Res 50:177–182.

Jain RC, Vyas CR. 1975. Garlic in alloxan-induced diabetic rabbits. Am J Clin Nutr 28:684–685.

JECFA. 2006. Steviol glycosides (addendum to stevioside). In: FAO/WHO, editor. Safety evaluation of certain food additives: sixty-third meeting of the joint FAO/WHO expert on food additives. Geneva: WHO Food Additives Series.

Jeppesen PB, Gregersen S, Poulsen CR, Hermansen K. 2000. Stevioside acts directly on pancreatic beta cells to secrete insulin: actions independent of cyclic adenosine monophosphate and adenosine triphosphate-sensitive K+-channel activity. Metabolism 49:208–214.

Karunanayake EH, Welihinda J, Sirimanne SR, Sinnadorai G. 1984. Oral hypoglycaemic activity of some medicinal plants of Sri Lanka. J Ethnopharmacol 11:223–231.

Khan A, Bryden NA, Polansky MM, Anderson RA. 1990. Insulin potentiating factor and chromium content of selected foods and spices. Biol Trace Elem Res 24:183–188.

Khan A, Safdar M, Ali Khan MM, Khattak KN, Anderson RA. 2003. Cinnamon improves glucose and lipids of people with type 2 diabetes. Diabetes Care 26:3215–3218.

Khan BA, Abraham A, Leelamma S. 1995. Hypoglycemic action of *Murraya koenigii* (curry leaf) and *Brassica juncea* (mustard): mechanism of action. Indian J Biochem Biophys 32:106–108.

Khare AK, Tondon RN, Tewari JP. 1983. Hypoglycaemic activity of an indigenous drug (*Gymnema sylvestre*, 'Gurmar') in normal and diabetic persons. Indian J Physiol Pharmacol 27:257–258.

Kiesewetter H, Jung F, Pindur G, Jung EM, Mrowietz C, Wenzel E. 1991. Effect of garlic on thrombocyte aggregation, microcirculation, and other risk factors. Int J Clin Pharmacol Ther Toxicol 29:151–155.

Kinghorn AD, Soejarto DD. 2002. Discovery of terpenoid and phenolic sweeteners from plants. Pure Appl Chem 74: 1169–1179.

Kirkham S, Akilen R, Sharma S, Tsiami A. 2009. The potential of cinnamon to reduce blood glucose levels in patients with type 2 diabetes and insulin resistance. Diabetes Obes Metab 11: 1100–1113.

Kook S, Kim GH, Choi K. 2009. The antidiabetic effect of onion and garlic in experimental diabetic rats: meta-analysis. J Med Food 12:552–560.

Leung L, Birtwhistle R, Kotecha J, Hannah S, Cuthbertson S. 2009. Anti-diabetic and hypoglycaemic effects of *Momordica charantia* (bitter melon): a mini review. Br J Nutr 102:1703–1708.

Lungarini S, Aureli F, Coni E. 2008. Coumarin and cinnamaldehyde in cinnamon marketed in Italy: a natural chemical hazard? Food Addit Contam Part A Chem Anal Control Expo Risk Assess 25:1297–1305.

Marinangeli CP, Jones PJ. 2010. Functional food ingredients as adjunctive therapies to pharmacotherapy for treating disorders of metabolic syndrome. Ann Med 42:317–333.

Mitchell HL, Aggett PJ, Richardson DP, Stowell JD. 2010. Food & health forum meeting: evidence-based nutrition. Br J Nutr 105: 322–328.

Mollet B, Rowland I. 2002. Functional foods: at the frontier between food and pharma. Curr Opin Biotechnol 13:483–485.

Murakami N, Murakami T, Kadoya M, Matsuda H, Yamahara J, Yoshikawa M. 1996. New hypoglycemic constituents in "gymnemic acid" from *Gymnema sylvestre*. Chem Pharm Bull (Tokyo) 44:469–471.

Ogden CL, Carroll MD, Curtin LR, Lamb MM, Flegal KM. 2010. Prevalence of high body mass index in US children and adolescents, 2007-2008. JAMA 303:242–249.

Ohnishi Y, Takagi S, Miura T, Usami M, Kako M, Ishihara E, et al. 1996. Effect of ginseng radix on GLUT2 protein content in mouse liver in normal and epinephrine-induced hyperglycemic mice. Biol Pharm Bull 19:1238–1240.

Okabayashi Y, Tani S, Fujisawa T, Koide M, Hasegawa H, Nakamura T, et al. 1990. Effect of *Gymnema sylvestre*, R Br. on glucose homeostasis in rats. Diabetes Res Clin Pract 9:143–148.

Ooi CP, Yassin Z, Hamid TA. 2010. *Momordica charantia* for type 2 diabetes mellitus. Cochrane Database Syst Rev, CD007845.

Pasupuleti VK, Anderson JM. 2008. Nutraceuticals, glycemic health and type 2 diabetes. Oxford, UK: Wiley-Blackwell.

Peng X, Cheng KW, Ma J, Chen B, Ho CT, Lo C, et al. 2008. Cinnamon bark proanthocyanidins as reactive carbonyl scavengers to prevent the formation of advanced glycation end products. J Agric Food Chem 56:1907–1911.

Pradeepa R, Mohan V. 2002. The changing scenario of the diabetes epidemic: implications for India. Indian J Med Res 116: 121–132.

Qin B, Dawson H, Polansky MM, Anderson RA. 2009. Cinnamon extract attenuates TNF-alpha-induced intestinal lipoprotein ApoB48 overproduction by regulating inflammatory, insulin, and lipoprotein pathways in enterocytes. Horm Metab Res 41: 516–522.

Qin B, Panickar KS, Anderson RA. 2010. Cinnamon: potential role in the prevention of insulin resistance, metabolic syndrome, and type 2 diabetes. J Diabetes Sci Technol 4:685–693.

Raju J, Gupta D, Rao AR, Yadava PK, Baquer NZ. 2001. *Trigonellafoenum graecum* (fenugreek) seed powder improves glucose homeostasis in alloxan diabetic rat tissues by reversing the altered glycolytic, gluconeogenic and lipogenic enzymes. Mol Cell Biochem 224:45–51.

Rasnake CM, Trumbo PR, Heinonen TM. 2008. Surrogate endpoints and emerging surrogate endpoints for risk reduction of cardiovascular disease. Nutr Rev 66:76–81.

Reeds DN, Patterson BW, Okunade A, Holloszy JO, Polonsky KS, Klein S. 2011. Ginseng and ginsenoside Re do not improve beta-cell function or insulin sensitivity in overweight and obese subjects with impaired glucose tolerance or diabetes. Diabetes Care 34:1071–1076.

Renwick AG. 2008. The use of a sweetener substitution method to predict dietary exposures for the intense sweetener rebaudioside A. Food Chem Toxicol 46(Suppl 7):S61–S69.

Roberfroid MB. 2000. A European consensus of scientific concepts of functional foods. Nutrition 16:689–691.

Roman-Ramos R, Flores-Saenz JL, Alarcon-Aguilar FJ. 1995. Anti-hyperglycemic effect of some edible plants. J Ethnopharmacol 48:25–32.

Sabbe S, Verbeke W, Deliza R, Matta V, Van Damme P. 2009. Effect of a health claim and personal characteristics on consumer acceptance of fruit juices with different concentrations of acai (*Euterpe oleracea* Mart.). Appetite 53:84–92.

Shanmugasundaram ER, Gopinath KL, Radha Shanmugasundaram K, Rajendran VM. 1990a. Possible regeneration of the islets of Langerhans in streptozotocin-diabetic rats given *Gymnema sylvestre* leaf extracts. J Ethnopharmacol 30:265–279.

Shanmugasundaram ER, Rajeswari G, Baskaran K, Rajesh Kumar BR, Radha Shanmugasundaram K, Kizar Ahmath B. 1990b. Use of *Gymnema sylvestre* leaf extract in the control of blood glucose in insulin-dependent diabetes mellitus. J Ethnopharmacol 30: 281–294.

Shanmugasundaram KR, Panneerselvam C, Samudram P, Shanmugasundaram ER. 1983. Enzyme changes and glucose utilisation in diabetic rabbits: the effect of *Gymnema sylvestre*. R Br J Ethnopharmacol 7:205–234.

Sharma RD, Raghuram TC, Rao NS. 1990. Effect of fenugreek seeds on blood glucose and serum lipids in type I diabetes. Eur J Clin Nutr 44:301–306.

Shaw JE, Sicree RA, Zimmet PZ. 2010. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract 87:4–14.

Shimizu K, Ozeki M, Tanaka K, Itoh K, Nakajyo S, Urakawa N, Atsuchi M. 1997. Suppression of glucose absorption by extracts from the leaves of Gymnema inodorum. J Vet Med Sci 59: 753–757.

Sievenpiper JL, Sung MK, Di Buono M, Seung-Lee K, Nam KY, Arnason JT, et al. 2006. Korean red ginseng rootlets decrease acute postprandial glycemia: results from sequential preparation- and dose-finding studies. J Am Coll Nutr 25:100–107.

Sitprija S, Plengvidhya C, Kangkaya V, Bhuvapanich S, Tunkayoon M. 1987. Garlic and diabetes mellitus phase II clinical trial. J Med Assoc Thai 70(Suppl 2):223–227.

Srinivasan K. 2005. Plant foods in the management of diabetes mellitus: spices as beneficial antidiabetic food adjuncts. Int J Food Sci Nutr 56:399–414.

Suksomboon N, Poolsup N, Boonkaew S, Suthisisang CC. 2011. Meta-analysis of the effect of herbal supplement on glycemic control in type 2 diabetes. J Ethnopharmacol 137:1328–1333.

Suzuki Y, Ito Y, Konno C, Furuya T. 1991. Effects of tissue cultured ginseng on gastric secretion and pepsin activity. Yakugaku Zasshi 111:770–774.

Ten Have M, de Beaufort ID, Teixeira PJ, Mackenbach JP, van der Heide A. 2011. Ethics and prevention of overweight and obesity: an inventory. Obes Rev 12:669–679.

Thomas J. 2010. Stevia: it's not just about calories. Open Obes J 2: 101–109.

Tjokroprawiro A, Pikir BS, Budhiarta AA, Pranawa, Soewondo H, Donosepoetro M, et al. 1983. Metabolic effects of onion and green beans on diabetic patients. Tohoku J Exp Med 141: 671–676.

Trumbo PR, Ellwood KC. 2006. Chromium picolinate intake and risk of type 2 diabetes: an evidence-based review by the United States Food and Drug Administration. Nutr Rev 64:357–363.

Uebanso T, Arai H, Taketani Y, Fukaya M, Yamamoto H, Mizuno A, et al. 2007. Extracts of *Momordica charantia* suppress postprandial hyperglycemia in rats. J Nutr Sci Vitaminol (Tokyo) 53: 482–488.

Vuksan V, Sievenpiper JL. 2005. Herbal remedies in the management of diabetes: lessons learned from the study of ginseng. Nutr Metab Cardiovasc Dis 15:149–160.

Waki I, Kyo H, Yasuda M, Kimura M. 1982. Effects of a hypoglycemic component of ginseng radix on insulin biosynthesis in normal and diabetic animals. J Pharmacobiodyn 5: 547–554.

Wheeler A, Boileau AC, Winkler PC, Compton JC, Prakash I, Jiang X, Mandarino DA. 2008. Pharmacokinetics of rebaudioside A and stevioside after single oral doses in healthy men. Food Chem Toxicol 46(Suppl 7):S54–S60.

WHO. 1985. Diabetes mellitus: report of a WHO Study Group, Technical Report Series.

World Health Organization. Diabetes (WHO). 2008. The cost of diabetes. WHO. Fact sheet N. 312, Nov 2008. Online edition.

Yeh GY, Eisenberg DM, Kaptchuk TJ, Phillips RS. 2003. Systematic review of herbs and dietary supplements for glycemic control in diabetes. Diabetes Care 26:1277–1294.

Yoon KH, Lee JH, Kim JW, Cho JH, Choi YH, Ko SH, et al. 2006. Epidemic obesity and type 2 diabetes in Asia. Lancet 368: 1681–1688.

Yoshikawa M, Murakami T, Matsuda H. 1997. Medicinal foodstuffs. X. Structures of new triterpene glycosides, gymnemosides-c, -d, -e, and -f, from the leaves of *Gymnema sylvestre* R. Br.: influence of gymnema glycosides on glucose uptake in rat small intestinal fragments. Chem Pharm Bull (Tokyo) 45:2034–2038.

Yuan CS, Wu JA, Lowell T, Gu M. 1998. Gut and brain effects of American ginseng root on brainstem neuronal activities in rats. Am J Chin Med 26:47–55.