

# Functional herbal food ingredients used in type 2 diabetes mellitus

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Submitted: 15-11-2010

Revised: 15-11-2010

Published: 08-05-2012

## ABSTRACT

From many reports it is clear that diabetes will be one of the major diseases in the coming years. As a result there is a rapidly increasing interest in searching new medicines, or even better searching prophylactic methods. Based on a large number of chemical and pharmacological research work, numerous bioactive compounds have been found in functional herbal food ingredients for diabetes. The present paper reviews functional herbal food ingredients with regards to their anti-diabetic active principles and pharmacological test results, which are commonly used in Asian culinary system and medical system and have demonstrated clinical or/and experimental anti-diabetic effectiveness. Our idea of reviewing this article is to give more attention to these functional food ingredients as targets medicinal foods in order to prevent or slow down the development of type 2 diabetes mellitus.

**Key words:** Anti-diabetic, functional herbal food, type 2 diabetes mellitus

## INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a global epidemic with an estimated worldwide prevalence of 6% (246 million people) in 2007, and forecast to rise to 7.3% (380 million) by 2025.<sup>[1]</sup> The health, social, and economic burden is great;<sup>[2,3]</sup> consequently, T2DM presents a major challenge to healthcare systems around the world.

Based on current understanding of the pathophysiology of T2DM, multiple pharmacological and non-pharmacological interventions have been developed over the past five decades with the aim of improving glycemic control and hopefully slowing disease progression.<sup>[4]</sup> To an extent, there has been some disappointment, in that most of the observed initial improvements in glycemic control are not sustained because of the progressive nature of the disease.<sup>[5,6]</sup> With the presence of more approaches to improve glycemic control using treatments,

the target on food conservation for people becomes even more important.

This article particularly explores the demonstrated clinical or/and experimental anti-diabetic functional food ingredients that prevents or slows down the development of T2DM. Especially T2DM requires the adoption and maintenance of multiple self-care behaviors to achieve and sustain glycemic control. These behaviors include monitoring blood glucose, exercising regularly, and adhering to a recommended eating regimen. Eating is a major aspect of daily living, one that may influence the development of diabetes and its subsequent progression.<sup>[7]</sup> Therefore we suggest that it is important to pay close attention to these review functional food ingredients for preventive and curative of T2DM and its complications.

## TYPE 2 DIABETES

Most patients, previously called as non-insulin-dependent diabetes mellitus (NIDDM), belong to this category. In this type, the mass of pancreatic  $\beta$  cells and their function are preserved to some extent, and insulin injection is seldom needed to sustain life.<sup>[8,9]</sup> Ketoacidosis could occur, however, in the presence of severe infection or other stress. This type also decreases insulin secretion and decreased insulin sensitivity (insulin resistance) is involved in its pathogenesis. Insulin resistance may not always be present. The relative role of these two factors varies between patients. With regard to insulin secretion, the acute insulin response to a glucose load is characteristically defective. The majority of patients is obese or has been obese in the past.

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### Access this article online

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#### DOI:

10.4103/0973-7847.95863

Typically, this type of diabetes develops after middle age, but may occur in younger people. Screening by urinalysis of large numbers of schoolchildren has revealed that T2DM has been steadily increasing since the 1970s.<sup>[10]</sup>

### Complimentary medicine aspects of diabetes

Nowadays, besides conventional approaches, comprehensive complementary medicine (CAM) modalities are attaining more and more popularity in the world.<sup>[11]</sup> More than 2000 years ago, symptoms such as polyuria and polydipsia were regarded as important morbid manifestations in ancient China and some other parts of the world, which spurred people to learn about diabetes.<sup>[12,13]</sup> It has long been utilized across the long Chinese history to treat a complex of symptoms, which manifests the disease of “diabetes mellitus” as Western medicine terms it.<sup>[14,15]</sup> Thus the ancient disease “wasting thirst” (xiao-ke), which probably equates to the term “diabetes” in Western medicine, was formed in that special way.<sup>[16]</sup> T2DM was recognized as xiaokezheng (a disease with symptomatic polydipsia) in ancient China.<sup>[17]</sup>

Symptoms that included polyuria and polydipsia were described in the Egyptian Ebers papyri, Greek Epidemics Book III of Hippocrates, and the Chinese Nei Ching.<sup>[18,19]</sup> Hindu writings in the Ayurvedic texts used these same symptoms and others including glucosuria and the smell of breath acetone to differentiate two main types of diabetes mellitus: One inherited and another acquired through obesity.<sup>[20]</sup> Recorded treatments for these disorders included largely diet- and plant-based remedies.<sup>[20,21]</sup>

### Concepts of functional foods

The term “functional food” was first introduced in Japan in the mid-1980s and refers to foods containing ingredients that aid specific bodily functions in addition to being nutritious.<sup>[22]</sup> Generally, they are considered as those foods intended to be constituted as part of a normal diet, and that contain biologically active components, which offer the potential of enhanced health or reduced risk of disease.<sup>[23]</sup>

Research has demonstrated that nutrition plays a crucial role in the prevention of chronic diseases like diabetes, as most of them can be related to diet.<sup>[23]</sup> Functional food enters the concept of considering food not only necessary for living but also as a source of mental and physical well-being, contributing to the prevention and reduction of risk factors for several diseases or enhancing certain physiological functions.<sup>[24]</sup> A food can be regarded as functional if it is satisfactorily demonstrated to affect beneficially one or more target functions in the body, beyond adequate nutritional effects, in a way which is relevant to either the state of well-being and health or reduction of the risk of a disease. The beneficial effects could be either maintenance or promotion of a state of well-being or health and/or a reduction of risk of a pathologic process or a disease.<sup>[25]</sup> The increasing interest in functional food reflects the fact that epidemiological studies indicating a specific diet or component of the diet is associated with a lower risk for a certain disease like diabetes.

### Functional herbal food ingredients used in diabetes *Allii Sativi Bulbus*

The bulbs of *Allium sativum* L., has a very long folk history of use in a wide range of ailments. It is also alleged to help regulate blood sugar levels. It can reduce glucose metabolism in diabetics, slows the development of arteriosclerosis and lowers the risk of further heart attacks in myocardial infarct patients.<sup>[26]</sup> Garlic has been found to be effective in lowering serum glucose levels in STZ-induced as well as alloxan-induced diabetic rats and mice. Most of the studies showed that garlic can reduce blood glucose levels in diabetic mice, rats, and rabbits.<sup>[27]</sup> Aged garlic extract was also effective in preventing hyperglycemia in mice hyperglycemic by immobilization stress.<sup>[28]</sup> In addition, Liu *et al* 2005 reported that both garlic oil and diallyl trisulfide improved glycemic control in STZ-induced diabetic rats.<sup>[29]</sup> Intake of garlic juice resulted in better utilization of glucose in glucose tolerance tests performed in rabbits, while allicin at a dose of 250 mg/kg was 60% as effective as tolbutamide in alloxan-induced diabetic rabbits.<sup>[30]</sup>

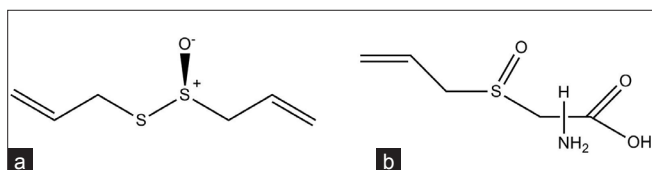
Mechanism of garlic has previously suggested that allicin can enhance serum insulin by effectively combining with compounds like cysteine, which would spare insulin from SH group reactions that are a common cause of insulin inactivation.<sup>[30]</sup> Another mechanism proposed that the antioxidant effect of S-allyl cysteine sulfoxide, an isolated product from garlic, may contribute to its beneficial effect in diabetes.<sup>[31]</sup> Another researcher postulated that garlic may act as an antidiabetic agent by increasing either the pancreatic secretion of insulin from the  $\beta$  cells or release of bound insulin.<sup>[32]</sup> Therefore the hypoglycemic action of garlic could possibly be due to an increase in pancreatic secretion of insulin from  $\beta$  cells, release of bound insulin or enhancement of insulin sensitivity [Figure 1].

### *Allii Cepa Bulbus*

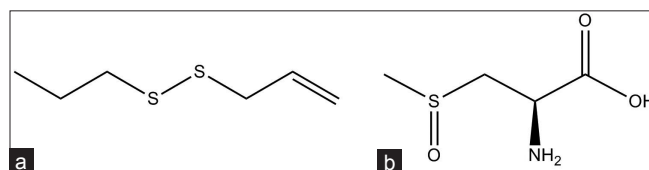
The bulbs of *Allium cepa* L. or common onion has a long history of medicinal and culinary use.<sup>[33]</sup> Also it has been used for many centuries for their pungency and flavoring value, for its medicinal properties.<sup>[34]</sup> Many people in Asian and African countries use plants for the treatment of diabetes.<sup>[35]</sup> Onion feeding improved the metabolic status in diabetic conditions, probably because of hypoglycemic and hypo-cholesterolemic effect,<sup>[36]</sup> mediated diabetic nephropathy by lowering blood cholesterol levels and decreasing lipid peroxidation.<sup>[37]</sup> Its active principles showed that allyl propyl disulfide and S-methyl cysteine sulfoxide have an anti-diabetic and anti-hyperlipidemic effect, the latter being analogous to glibenclamide and insulin [Figure 2].<sup>[38-40]</sup>

### *Trigonella foenum-graecum* (L.)

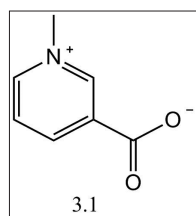
*Trigonella foenum-graecum* L. (fenugreek) is cultivated throughout India and in certain regions of China. Its seeds are used as condiment in India, a supplement to wheat and maize flour for bread-making in Egypt, and one of the staple foods in Yemen. Its seeds are also used as herbal medicine in many parts of the world for their carminative, tonic, and aphrodisiac effects. Various reports have demonstrated that fenugreek seeds extracts, powder, and gum of seeds and leaves can lower blood glucose



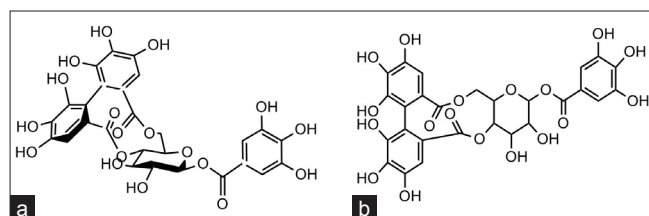
**Figure 1:** Chemical components in *Allium sativum* L. which involve in anti-hyperglycemic activity. (a) Allicin; (b) S-allyl cysteine sulfoxide



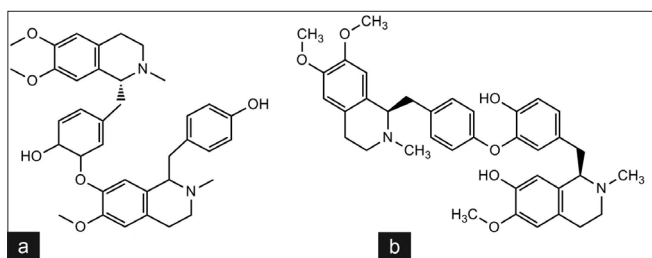
**Figure 2:** Chemical components in *Allium cepa* L. which involve in anti-hyperglycemia. (a) Allyl propyldisulfide; (b) S-methyl cysteine sulfoxide



**Figure 3:** Chemical components in *Trigonella foenum-graecum* L. which involve in anti-hyperglycemia. (a) Trigonelline



**Figure 4:** Chemical components in *Psidium guajava* L., which involve in anti-hyperglycemia. (a) Strictinin; (b) Pedunculagin



**Figure 5:** Chemical components in *Nelumbo nucifera* Gaertn. which involve in anti-hyperglycemia. (a) Liensinine; (b) Daurisoline

and cholesterol levels in human and experimental diabetic animals.<sup>[41-45]</sup> Its activity has been attributed largely to saponins,<sup>[46]</sup> high-fiber content,<sup>[47]</sup> the amino acid 4-hydroxyisoleucine,<sup>[48]</sup> and the major alkaloid trigonelline [Figure 3].<sup>[49]</sup>

### *Psidium guajava* (L.)

*Psidium guajava* L. is a semi-deciduous tropical tree and is widely grown throughout India for its fruit called Guava. Its fruits are rich in dietary fiber associated with natural antioxidant compounds.<sup>[50]</sup> The fruit contains a high percentage of vitamin C, carotene, vitamin B1, B2, B6, and pectin.<sup>[51]</sup> The extract of the whole plant of *P. guajava* excluding roots was reported to be devoid of any antibacterial, antifungal, antiviral, anti-fertility, hypoglycemic, diuretic, and anti-inflammatory activities.<sup>[52]</sup> Recently, the ripe fruit peel has been found to possess hyperglycemic activity in diabetic patients.<sup>[53]</sup> Antidiabetic activity based on higher concentration of Mg in the raw fruit peel of *P. guajava* had been found.<sup>[54]</sup> The leaves of *P. guajava* inhibit the increase of plasma sugar level in alloxan-induced diabetic rats, during glucose tolerance test.<sup>[55]</sup> Flavonoid glycosides such as strictinin, isostrictinin, and pedunculagin are the effective constituents, which have been used in clinical treatment of diabetes to improve the sensitivity of insulin [Figure 4].<sup>[55]</sup>

### *Nelumbo nucifera* (Gaertn.)

*Nelumbo nucifera* Gaertn. is a useful medicinal culinary plant. It

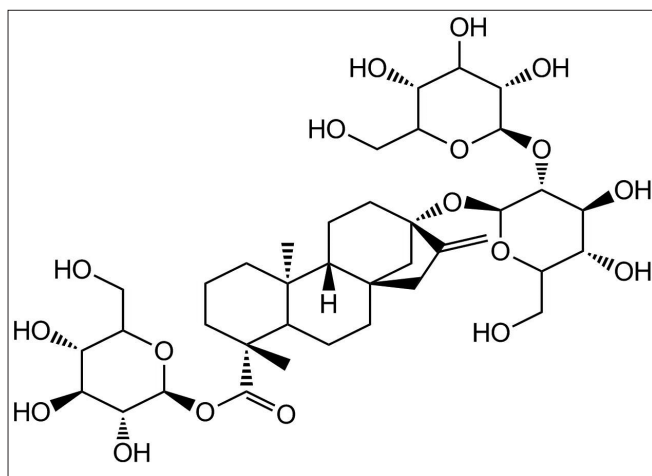
has been reported that rhizome extract showed anti-diabetic and anti-inflammatory effects.<sup>[56,57]</sup> On the other hands; it has recently been used as plain extraction or blend tea to treat obesity in China.<sup>[57,58]</sup> Alkaloids isolated from *Nelumbo nucifera*, including liensinine, daurisoline, neferine, and flavonoids are the main compounds that give medicinal effects [Figure 5].<sup>[59-61]</sup>

### *Stevia rebaudina* (Bert.) Hemsl.

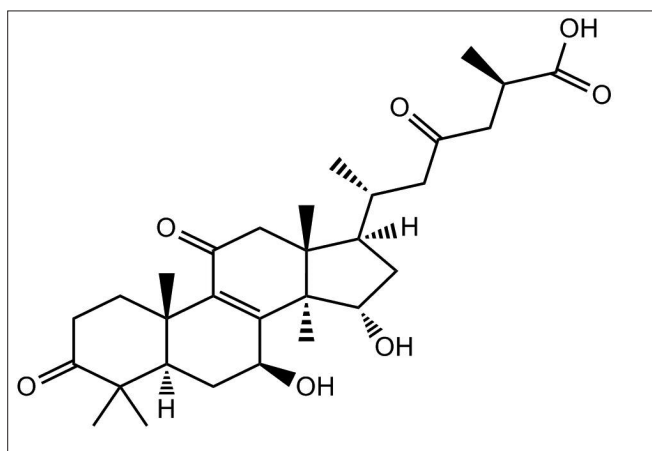
*Stevia rebaudina* (Bert.) Hemsl. has been used in the treatment of diabetes for many years in China and some other parts of the world. In China this plant is used in medicinal teas for treating heartburn and other ailments also. Plant contain stevioside sweetener that reduces postprandial blood glucose levels in T2DM patients, indicating beneficial effects on the glucose metabolism.<sup>[62]</sup> The plant contain stevioside with the mechanism to stimulate insulin secretion via a direct action on  $\beta$  cells of pancreatic islet, which is considered to have the potential of becoming a new anti-diabetic drug for use in T2DM [Figure 6].<sup>[63,64]</sup>

### *Prunella vulgaris* (L.)

Dried *Prunella vulgaris* L., is used to make herbal drink to help restore the body to a natural state after eating too many fried foods. It can be used in salads, soups, stews, or boiled as a pot herb. For medicinal purposes, the whole plant is gathered when the flowers bloom, and dried. It has been reported that there is anti-hyperglycemic effect of the ethanol extract of *Prunella vulgaris* L. in mice.<sup>[65]</sup> Compound Jiangtangsu had been isolated from this plant and confirmed to have a remarkable effect to lower blood sugar levels in mice with diabetes mellitus induced by alloxan.<sup>[66]</sup> The possible mechanism of Jiangtangsu is to repair  $\beta$  cells of pancreatic islet to release insulin. Constituents in the *P. vulgaris* have been identified, such as, phenolic acids (rosmarinic, caffeic), triterpenoids (methyl oleanolate, methyl ursolate, methyl maslinate),<sup>[67-69]</sup> flavonoids (quercetin, campherol, rutin),<sup>[70]</sup> tannins, and polysaccharide.<sup>[71,72]</sup> The anti-hyperglycemic activity of the *P. vulgaris* may be due to any one or more of the above constituents [Figure 7].



**Figure 6:** Chemical components in *Stevia rebaudina* (Bert.) Hemsl., which involve in anti-hyperglycemia, Stevioside



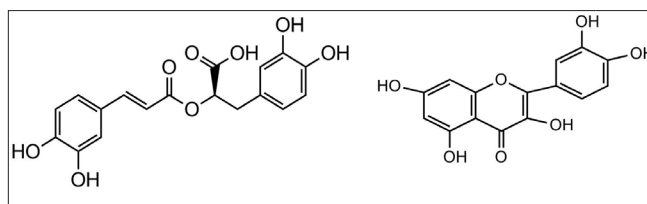
**Figure 8:** Chemical components in *Ganoderma lucidum* (Leyss. Ex Franch.), which involve in anti-hyperglycemia, Ganoderic acid

### *Ganoderma lucidum* (Leyss., ex. Fr.)

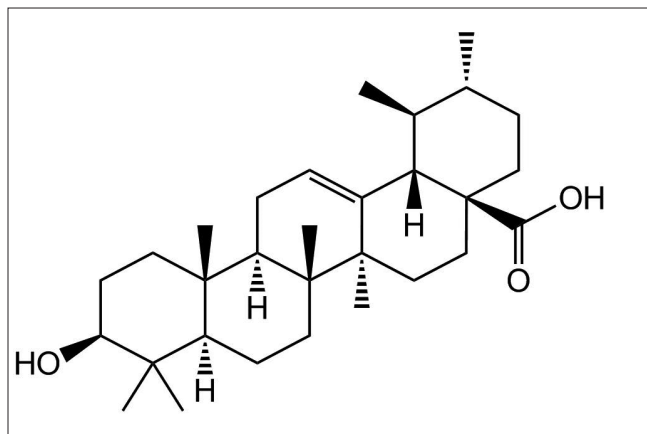
Mushrooms have a notable place in the folklore throughout the world and in the traditions of many cultures.<sup>[73]</sup> *Ganoderma lucidum* is commonly known as a medicinally potent mushroom. It has been widely used in China and other oriental countries for hundreds of years for the treatment of various diseases, including diabetes and cancer. The sporophore of *Ganoderma lucidum* is used as both tonic nourishment and medicine for care of diabetic patients. Some research results showed that polysaccharides are the active principles for anti-diabetes.<sup>[74,75]</sup> Ganoderans A and B have been isolated and confirmed to have a hypoglycemic activity [Figure 8].<sup>[76,77]</sup>

### *Punica granatum* (L.)

*Punica granatum* (Pomegranate) is a fruit-bearing deciduous shrub or small tree with diverse pharmacological and therapeutic effects.<sup>[78]</sup> Pericarpium Granati is used to treat diabetes mellitus in some parts of China. Male abortive flowers of *Punica granatum* are also used for the treatment of diabetes mellitus in India. Oral administration of the aqueous ethanolic extract of *Punica*



**Figure 7:** Chemical components in *Prunella vulgaris* L., which involve in anti-hyperglycemia. (a) Rosmarinic acid; (b) Quercetin



**Figure 9:** Chemical components in *Punica granatum* L., which involve in anti-hyperglycemia, Ursolic acid

*granatum* flowers led to a significant blood glucose lowering effect in normal, glucose fed and alloxan-induced diabetic rats.<sup>[79]</sup> The extract of *Punica granatum* seeds was also reported to have antidiabetic activity; ursolic acid may be the active constituent [Figure 9].<sup>[80]</sup>

### *Dioscorea opposita* (Thunb.)

*Dioscorea opposita*, “Chinese yam”, is native to China. The rhizomes of *Dioscorea opposita* Thunb., was traditionally used in diets to control Xiaokezheng (diabetes) in China. Researches confirmed that the water decoction of *Dioscorea opposita* has an anti-hyperglycemic effect to experimental diabetic mice.<sup>[81]</sup> Polysaccharides were considered to be the active constituents. Chemical component of *Dioscorea opposita*, dioscin and diosgenin may be the cause for medicinal effects [Figure 10].<sup>[82]</sup>

### *Momordica charantia* (L.)

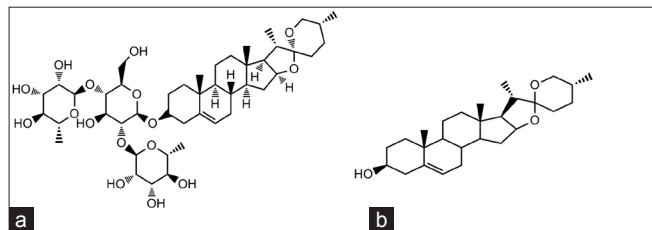
*Momordica charantia* L. is not only a nutritious vegetable, but is also used in traditional medical practices to treat T2DM. Experimental studies with animals and humans suggested that the vegetable has a possible role in glycemic control. Oral administration of the extract, fruit juice or seed powder of *Momordica charantia* caused a significant reduction in fasting blood glucose and improved glucose tolerance in normal and diabetic animals and in humans.<sup>[83-89]</sup> A wide range of compounds have been isolated from *Momordica charantia*, of which, a polypeptide (p-insulin, was named as “plant insulin”), the sterol glucoside mixture charantin and the pyrimidine nucleoside vicine have been identified as the orally anti-diabetic principles for humans and animals [Figure 11].<sup>[90,91]</sup>

### *Murraya koenigii* (L.)

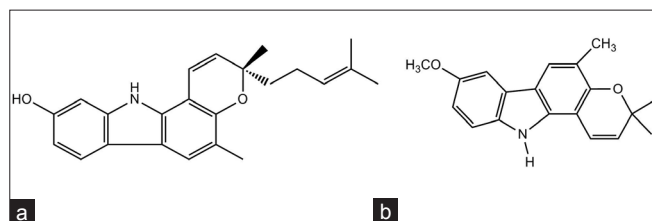
*Murraya koenigii* L. is promising as it is widely and regularly used as a spice for food flavoring and as such it appears to be without any side effects and toxicity. It is also popular in medical usage. Eating, fully-grown curry leaves is beneficial in controlling diabetes and in weight loss. The leaves of *Murraya koenigii* are also used as a herb in Indian medicine. Their properties include much value as an anti-diabetic and antioxidant.<sup>[92,93]</sup> The aqueous extract of *Murraya koenigii* leaves has been taken to evaluate the hypoglycemic activity in normal and alloxan-induced diabetic rabbits. The findings from this study suggested that the aqueous extract of these leaves may be prescribed as adjunct to dietary therapy and drug treatment for controlling diabetes mellitus.<sup>[94]</sup> An intense search of the literature has revealed that the stems, leaves, roots, and seeds are potential sources of carbazole alkaloids, which provide the medicinal effect. Some identified alkaloids are Koenimbine, Koenine, Koenigine, Koenidine, Mahanimbine and Mahanine<sup>[95-98]</sup> [Figure 12].

### *Artocarpus heterophyllus* (Lam.)

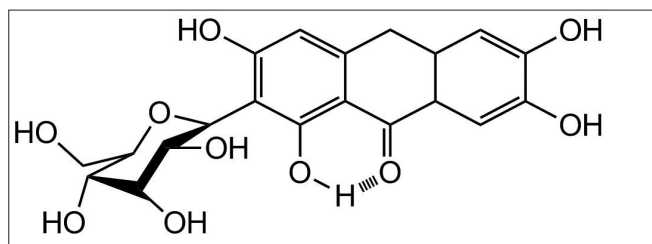
*Artocarpus heterophyllus* Lam. (jackfruit) is an integral part of common Indian diet and is freely available in Indian and adjoining continents, its medicinal properties are also mentioned in Indian medicine. The plant is reported to possess antibacterial, anti-inflammatory, anti-diabetic, antioxidant and immunomodulatory properties.<sup>[99]</sup>



**Figure 10:** Chemical component in *Dioscorea opposita* Thunb., which involve in anti-hyperglycemia. (a) Dioscin; (b) Diosgenin



**Figure 12:** Chemical components in *Murraya koenigii* L., which involve in anti-hyperglycemia. (a) Mahanine; (b) Koenimbine

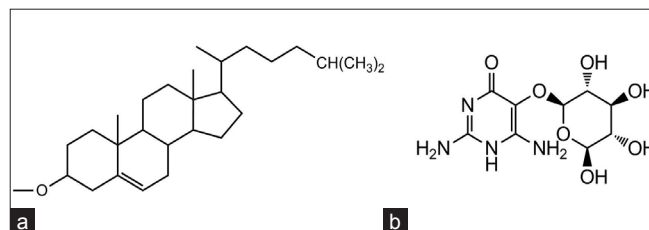


**Figure 14:** Chemical component in *Mangifera indica* Lam., which involve in anti-hyperglycemia, Mangiferin

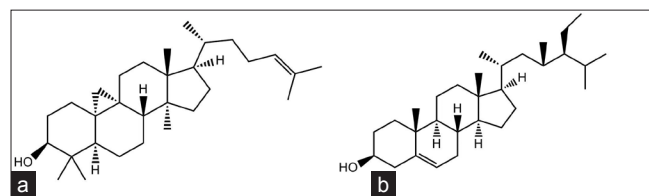
Hot water extract of mature jack leaves is recommended by Ayurvedic and traditional medical practitioners as a treatment for diabetes mellitus.<sup>[100]</sup> Previous studies have indicated that an extract of *Artocarpus heterophyllus* improves the glucose tolerance in normal human subjects and diabetic patients.<sup>[101]</sup> Its leaves contains hypoglycemic and hypolipidemic principles that have the potential to be developed further for the treatment of diabetes.<sup>[102]</sup> The leaves and stem show the presence of sapogenins, cycloartenone, cycloartenol,  $\beta$ -sitosterol, and tannins [Figure 13].<sup>[103]</sup>

### *Mangifera indica* (L.)

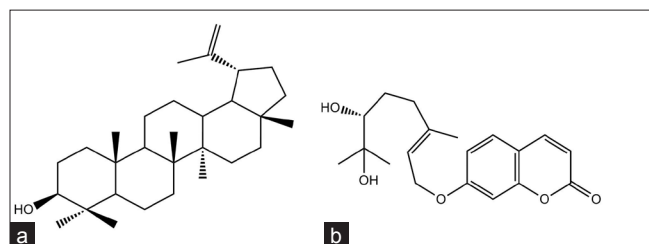
*Mangifera indica* is one of the most popular of all tropical fruits. Most parts of the tree [Fruit, seeds, pulp, stem bark, roots, and leaves] have medicinal properties.<sup>[104]</sup> It is native to tropical Asia. The leaves of *Mangifera indica* were proven for antidiabetic properties using normoglycemic, glucose-induced hyperglycemia and streptozotocin (STZ)-induced diabetic mice.<sup>[105]</sup> The natural C-glycoside xanthone mangiferin has been reported in various parts of *M. indica*, which gives the medicinal property.<sup>[106]</sup> In KK-A<sup>y</sup> mice, an animal model of type 2 diabetes, mangiferin (90 mg/kg), 7 h after oral administration, decreased the baseline glucose level by 56%.<sup>[107]</sup> In the same model, mangiferin (30 mg/kg, p.o., once daily followed 30 min. later by exercise (120 min motorized treadmill) for 2 weeks) reduced the blood cholesterol (~40%) and triglyceride levels (~70%) [Figure 14].<sup>[108]</sup>



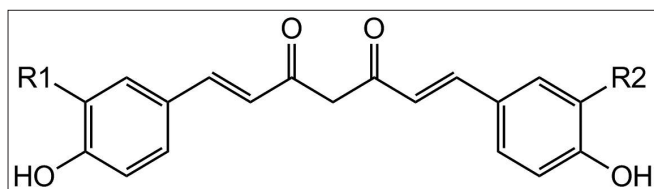
**Figure 11:** Chemical components in *Momordica charantia* L., which involve in anti-hyperglycemia. (a) Charantin; (b) Vicine



**Figure 13:** Chemical components in *Artocarpus heterophyllus* Lam., which involve in anti-hyperglycemia. (a) Cycloartenone; (b)  $\beta$ -sitosterol



**Figure 15:** Chemical components in *Aegle marmelos* L., which involve in anti-hyperglycemia. (a) Lupeol; (b) Marmin



**Figure 16:** Chemical components in *Curcuma longa* L., which involve in anti-hyperglycemia, Curcumin

### *Aegle marmelos* (L.) Corr.

*Aegle marmelos* (bael tree) fruit is eaten fresh or dried. As for other parts of the plant, the leaves and small shoots are eaten as salad greens in many Asian countries. It is a popular medicinal plant in the Ayurvedic and Siddha systems of medicine and folk medicines used to treat a wide variety of ailments.<sup>[109,110]</sup> The leaves, fruits, and stems contain skimianinc, sterol and aegelin, lupeol, marmin. In pharmacological trials, both the fruit and root showed anti-amoebic and hypoglycemic activities.<sup>[111-113]</sup> *A. marmelos* would act like insulin in the restoration of blood sugar and body weight to normal levels in rat and was therefore recommended as a potential hypoglycemic agent [Figure 15].<sup>[113]</sup>

### *Curcuma longa* (L.)

*Curcuma longa* L., commonly known as turmeric, has been used as spice and coloring agent with long history. Its rhizomes have been reported to possess anti-diabetic properties in experimental animal models.<sup>[114-116]</sup> Researches reported that active ingredient curcumin is the response for anti-diabetic action [Figure 16].<sup>[116]</sup>

## CONCLUSIONS

The development of T2DM is strongly influenced by eating practices. Also once diagnosed, a critical part of treatment is the modification of a lifetime of food and eating habits.<sup>[117]</sup> Functional herbal foods might have a particularly high impact for prevention or treatment of overweight and diabetes for which, more than in many other fields. Many of the elements found in the present review were identified in previous research about diabetes and functional food ingredients. However, the present research provided assistant for selecting of specific functional herbal food ingredients in the lives of people with T2DM and our normal day-to-day food consuming system to prevent such diseases.

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**How to cite this Article:** Perera PK, Li Y. Functional herbal food ingredients used in type 2 diabetes mellitus. *Phcog Rev* 2012; 6:37-45.

**Source of Support:** Nil, **Conflict of Interest:** None declared