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– SUPPORTS HEALTHY BLOOD SUGAR LEVELS –

– PROMOTES PROPER PANCREATIC FUNCTIONS –

– HELPS COMBATING INSULIN RESISTANCE –

THERAWIN

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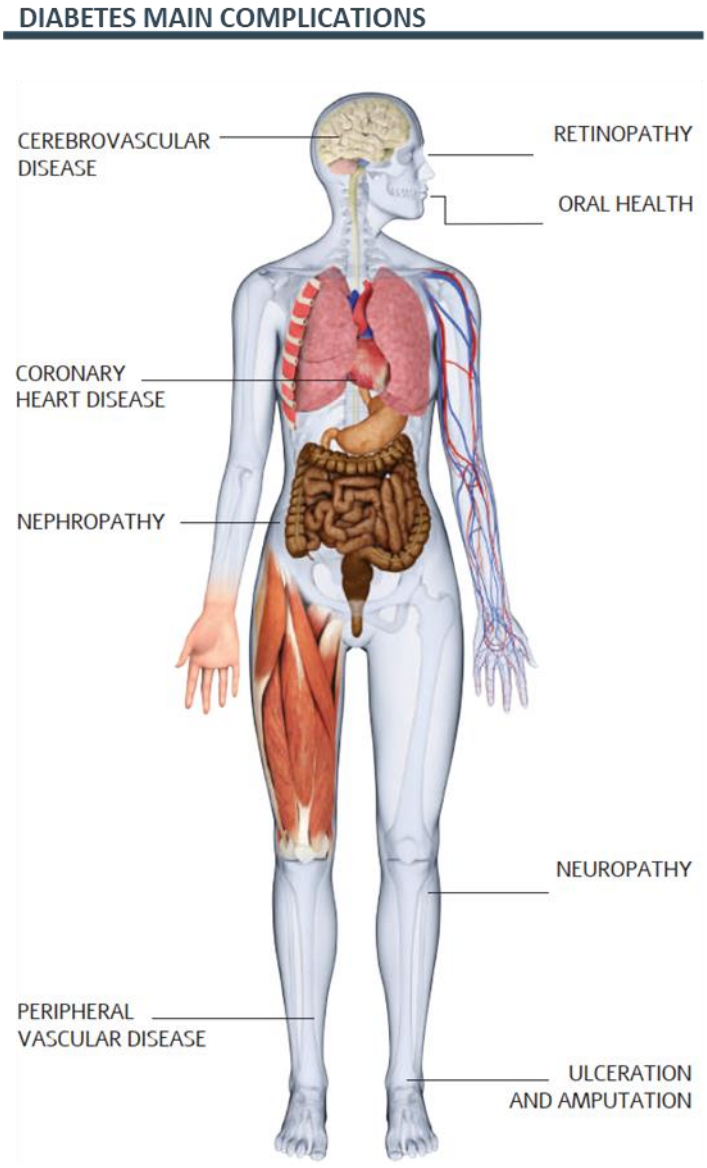
Herbal Food Supplement for Pre-Diabetes and Diabetes (Type 2)

Management of the Diabetic Profile Using Traditional Thai Pharmacopeia Plants

Diabetes: extent of the global phenomenon

Type 2 Diabetes (T2D), also referred to as Diabetes Mellitus type II or noninsulin dependent diabetes, is becoming a global health concern. Previously prevalent mostly in Western countries where it was associated with obesity and increase of processed food intake, with a morbidity rate estimated at over 10% of the general population, the epidemics has now reached South-East Asia and is spreading fast. In Thailand, it is estimated that T2D already affects 9.9% of the adult population [1]. Diabetes is becoming a leading cause of death in Thailand; of the more than 200,000 deaths annually due to chronic non-communicable diseases in the country, approximately 30,000 (15%) are due to diabetes [2]. With a prevalence estimated to 2.7% in 2002, 5.4% in 2012 and 6% in 2017, Vietnam sees a rapid increase of its population affected by the diseases [3]; some assume that by 2035, 16% of Vietnamese will suffer from T2D [4]. Similar trends are projected in Singapore with a prevalence in adults at 7.3% in 1990 and expected to reach 15% by 2050 [5]. And the disease tends to affect people at younger age, wide spreading among children and adolescents. Such projections can be made in all ASEAN countries, making T2D a real health concerns for the year to come in the region with severe complication for patients such as retinopathy, nephropathy, heart diseases, diabetes-associated tissue necrosis…



Etiology

What is diabetes and what are the mechanisms leading to the disease? In a normal physiological situation, glucose is absorbed by cells from the blood stream as a response to the release of insulin triggered by carbohydrate intake. A major part of the glucose present in the blood stream is absorbed by muscle and liver cells which store it as glycogen - an available glucose reserve between meals and during the overnight fast.

Insulin resistance

Our modern lifestyle with low levels of exercise (sedentary life) and diets rich in carbohydrates and hidden sugars exposes us to excess of sugar in the blood; the way for the body to cope with this is to release higher levels of insulin to absorb high levels of sugar. On the long term, this mechanism induces a decrease to insulin sensitivity (pre-diabetes phase) and then to insulin resistance. At that stage, even if the body releases more insulin, the cells do not respond to insulin signal and do not absorb sugar anymore; glycemia then remains high, this is diabetes. Prolonged high blood sugar levels harm blood vessels, especially:

- coronary arteries (risk of cardiac events),
- jugular veins (risk of cerebral vascular accidents),
- retinal blood vessels (risk of blindness),
- the kidney vessels (risk of kidney insufficiency),
- reproductive system vessels (risk of impotence).

Nerve fibres are also at risk of damages by high blood sugar, especially those responsible for sensation in the lower limbs.

An additional and significant impact of untreated diabetes is the appearance of diabetic ulcers. Initial symptoms appearing at the onset of diabetes include:

- increased thirst and dry mouth,
- frequent urination (mainly at night),
- strong urine odour,
- fatigue,
- a feeling of intense hunger between meals coupled with a drop in the level of glucose between meals as shown by sweating,
- nervousness,
- a rapid pulse and blurriness.

In addition, diabetes is associated with a chronic inflammation that can lead to damages to pancreatic insulin-producing cells. In the long-term, the body faces both insulin resistance and decreased insulin production.

As for many diseases, an early detection of diabetes, or preferably pre-diabetes, allows a better management of the disease.

However, today treatments are only given at diabetes stage. Most conventional medicines given orally are usually accompanied by side-effects and those given by injection have low patient compliance to treatments and/or decreased quality of life.

Action at the pre-diabetic stage would be an important part of T2D management as acting at this stage could (1) delay or prevent onset of diabetes, (2) be done with easier methods, i.e. food supplements, (3) induce fewer side effects than stronger drugs used in later stages of the disease.

Herbal medicine using traditional pharmacopeia

While western medicine has focused on the isolation of active ingredients that could be manufactured as small molecules using chemical engineering, traditional medicine based of the use of plants remained widespread in Asia.

Several plants are known to contain compounds that can have beneficial effects on several aspects of diabetes, regulation of sugar levels in the blood, decrease of insulin resistance, better glucose absorption by cells, protection of pancreas…

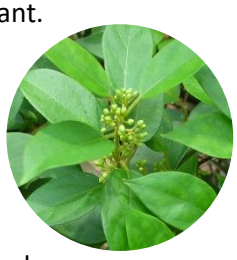
The most famous anti-diabetic plant is undoubtedly *Gymnema sylvestre*. This plant has been used in Ayurveda medicine to regulate blood sugar and to help in weight management and has some strong scientific evidence to back up such a use.

However, at Therawin, we think that combining several effects from several plants would be a better approach to act on different aspects underlying the diseases. Using an herbal mix, easily taken orally, is an easy way[1] for prediabetics and diabetics to help manage diabetes in addition to routine medicine.

Theralin™, a Unique Blend for Optimal Effect

Therawin has formulated a blend of herbs to maximise the effects of Theralin™.

Gymnema sylvestre ผักเชียงดา



Gymnema sylvestre might be the best known and most studied anti-diabetic plant. Its name in Indian, gurmar, literally means "*destroyer of sugar*". It has several interesting effects.

The gymnemic acid molecules are looking like glucose molecules; they can therefore fill the sugar receptors on the taste buds thereby preventing activation by sugar molecules present in the food, which prevents sugar craving. Using the same mechanism in the intestine, *Gymnema sylvestre* prevents sugar absorption by the intestine, which results in lower sugar levels in blood [6]. The plant extract induces significant reductions in fasting and post-meal blood sugar while stimulating insulin secretion by the pancreas β-cells [7].

The *Gymnema sylvestre*-triggered slow carbohydrate absorption rate from the digestive system also contributes to a longer feeling of satiety and participates in weight management, which is an important factor for T2D too.

➔ *Going further*

A study published in 2001 [8] examined how continuous daily consumption (90 days) of the *Gymnema* extracts affected the fasting blood glucose level; glucose measured two hours after a meal

[1] In addition to a healthy diet, with a limited intake of carbohydrates, a decent amount of fibres, and regular physical activity.

and the level of haemoglobin glycosylation (HbA1c). The study included 65 diabetics and demonstrated a statistically significant mean decreases:

- in fasting blood glucose by 11%,
- in 2-hour post-meal glucose by 13%
- in HbA1c rate by 0.6%.

Interestingly, in this study the highest effects were observed in patients with the poorest control of their glucose levels. It also appeared that the largest effect occurred from decrease of post-meal glucose levels. This is very positive as decreases in postprandial blood glucose significantly cause a decrease of HbA1c, therefore reducing the complications from diabetes.

Momordica charantia *มะระขี้นก*

The bitter melon or bitter gourd, widely used in Southeast Asia cuisines has been used traditionally for thousands of years for its medicinal properties. Some of the active ingredients of the bitter melon are vicine, charantin, triterpenoids and anti-oxidants that help reducing free radical levels [8]. In recent years many scientific studies analysed the anti-diabetic effects of *Momordica charantia* and showed that it could reduce haemoglobin glycosylation (HbA1c), 2-hour post meal glucose levels, glucose AUC and increment insulin AUC; showing a benefit on blood glucose regulation. In animal models, the use of *M. charantia* showed significant lowering of blood sugar [9] [10] and stimulation of insulin secretion [11]. It also showed protective and regenerative properties in insulin-secreting cells [12]. Some studies suggest that bitter melon can decrease insulin resistance in muscle cells and reduce the release of glucose in the bloodstream by the liver [13].

➔ *Going further*

A 2009 study conducted in Taiwan assessed the effects of bitter gourd extract on men and women with metabolic syndrome (abdominal obesity, dyslipidemia, hypertension and insulin resistance), which is a good predictor for high risks of T2D. The study concluded on the safety of the treatment in humans and demonstrated a significant (p=0.021) decrease of 19% in cases of the syndrome, associated with a decrease in waist circumference. The improved status remained for one month after treatment ended [14].

Trigonella Foenum-Graecum *ลูกซัด*

Fenugreek contains a high amount of fibres and alkaloids, which improve the ability of the pancreas to produce and release insulin mainly due to the presence of the amino acid 4-hydroxylisoleucine which regulates the release rate of insulin. Fenugreek also significantly acts on fasting blood sugar control and contributes to decreased of glycosylated haemoglobin [14].

Interestingly, besides its effects on blood sugar regulation and insulin secretion stimulation, fenugreek has been shown to significantly delay onset of T2D in individuals suffering from pre-diabetes [15].

➔ *Going further*

A study published in 2001 compared 12 newly diagnosed T2D patients receiving fenugreek extracts in addition to usual care to 13 other newly diagnosed T2D patients who received usual care and placebo over a period of 2 months [18]. Glucose AUC (2375 +/- 574 vs 27597 +/- 274) as well as insulin (2492 +/- 2536 vs. 5631 +/- 2428) were significantly lower ($p < 0.001$) in the group that had received fenugreek supplements. Insulin resistance also showed a decrease in the supplemented group while insulin sensitivity was increased (112.9 +/- 67 vs 92.2 +/- 57) ($p < 0.05$). Serum triglycerides decreased and high-density lipoprotein cholesterol ("good cholesterol") increased significantly in the fenugreek group as compared to the placebo group ($p < 0.05$). The study concluded on the beneficial adjunct use of fenugreek seeds to improve glycemic control and decrease insulin resistance in mild type-2 diabetic patients.

Curcuma longa ขมิ้นชัน

Turmeric is known for its culinary properties but also has been used for thousands of years in Asian medicines for its anti-inflammatory properties and in the treatment of diabetes. The active substance in turmeric, curcumin, is known for its ability to reduce Glucose levels and treat complications of diabetes [19] [20].

Similarly to fenugreek, the curcumin contained in curcuma is able to delay onset of T2D while improving function of insulin-secreting β-cells [21].

➔ *Going further*

The active mechanism of *Curcuma* is linked to its ability to moderate immune activity, namely down-modulating the NFκ-B pathway, and inhibiting the Tumour Necrosis Factor (TNF). NFκ-B and TNF are known to be involved in insulin resistance [22]. Another property includes raising sensitivity to insulin by the enzymatic activity of PPAR γ in muscle cells and fat [19] [21].

A double-blind study published in 2012 took a group of 120 subjects identified as pre-diabetics and examined how exposure to *Curcuma* supplement for 9 months might affect the rate at which the subjects condition deteriorated to diabetes. Parallel control group received a placebo throughout the duration of this period. In the group receiving the supplement, there was no event of deterioration occurring, while in the control group, over 16% were diagnosed as diabetic with lower levels of insulin secretion and high resistance to insulin [21], showing the potential of *Curcuma* in delaying onset of the disease.

Emblica officinalis มะขามป้อม

Through its antioxidant properties, Indian gooseberry has been reported to prevent/reduce hyperglycaemia and diabetic nephropathy [23] [20]. In a study evaluating the anti-diabetic and anti-cholesterol effects of Indian gooseberry fruits, diabetic patients showed a significant decrease of fasting and 2h post-meal blood sugar levels [25]. In this study, *Emblica officinalis* also showed to significantly reduce total cholesterol and triglycerides, improving high-density

lipoprotein cholesterol (“good cholesterol”) and lowering low-density lipoprotein cholesterol (“bad cholesterol”).

Due to its tannoid compounds, Indian gooseberry also acts on pancreatic cells functions. Animal studies showed clear histological changes in pancreatic tissues after intake [22].

Swertia chirata / Andrographis paniculata ฟ้าทะลาย

This plant grows mainly in the Himalayas and contains a number of active ingredients including chirtin, ophelic acid and mangiferin. Their properties include the direct activation of pancreatic cells to release insulin, the reduction of glucose absorption from the digestive system, improvement of the break-down process of cellular glucose (process of glycolysis) and an increase in the peripheral use of glucose by skeletal muscles and its storage in the liver and muscles.

Thanks to its flavonoid compounds, it is able to effectively prevent hyperglycaemia [23]. A study by Thomson *et al.* revealed that the antidiabetic actions of *Swertia chirata* aqueous bark extracts involves the stimulation of insulin secretion and enhancement of insulin action [28, 29].

Since *Swertia chirata* is becoming rare, some batches will contain *Andrographis paniculata* also known as green chiretta, that has the same properties as *Swertia* and that is a common substitute.

In rat models of type 2 diabetes, *Andrographis paniculata* showed significant antidiabetic and antihiperlipidemic effects that can be observed when using metformin [30, 31]. Leaf water extracts of the herbs were shown in other models to be effective in restoring the disturbed metabolic profile back to normal conditions in the obese diabetic rats, namely significant reduced blood glucose levels, and normalised levels of many metabolites related to hepatic function, fat metabolism etc. [32, 33]. Such effects are mainly due to andrographolide compounds. Interestingly, *Andrographis paniculata* has been shown to have beneficial effects on diabetes associated cognitive deficits [34]

Picrorhiza kurroa โกฐก้านพร้าว

In ayurvedic medicine, *Picrorhiza* is used for liver problems, fever, allergy, and many other conditions, its chemical compounds seem to have modulatory effects on the immune system and could relieve inflammation.

In recent animal model studies, *Picrorhiza* showed ability to regenerate insulin-secreting β-cells, thus enhancing production of insulin and control of glycemia [26]. The treatment with *Picrorhiza* extract induced significant reduction of fasting blood glucose levels in diabetic rats [27] [28]. Husain *et al.* showed that one mode of action of *Picrorhiza kurroa* was to increase the expression of the glucose transporter type 4 at the surface of skeletal muscle cells; this facilitates the uptake of glucose by the cells in presence of insulin [33].

Syzygium cumini ลูกหว้า

The Malabar, Java or black plum is effective in reducing blood glucose levels significantly and regulating the insulin levels [30]. This plant was traditionally used in Europe before the discovery of insulin to treat diabetes [31]. In several preclinical and clinical studies, many parts of the plant, especially fruits, seeds and stem bark, were reported for promising activity against diabetes [32]. Researchers in India have extracted a compound from the plant seeds called mycaminose and showed its anti-diabetic properties [33]. Leaf extracts have also been shown to act on the enzyme adenosine deaminase in diabetic patients and in turn reduce blood glucose levels [34].

Tinospora cordifolia ชิงช้าชาลี

According to some studies, extract of *Tinospora cordifolia* can act in an insulin-like way and help cells to uptake glucose, therefore reducing blood sugar levels [35].

In a clinical trial, the plant was found to have a synergistic and effective impact on Type 2 Diabetes management when given as add-on therapy to patients [36].

In another study in patients with diabetes-related foot ulcer, the plant was shown to be an interesting adjuvant therapy as its immunomodulatory properties helped wound healing [37].

➔ *Going further*

In an animal model of T2D, *Tinospora* showed to work through triggering insulin secretion and suppression of oxidative stress. It also restores cellular defence antioxidant markers in the liver. In the study, the treatment with *Tinospora* inhibited glucose 6-phosphatase and fructose 1,6-diphosphatase compared to placebo ($p < 0.001$); and restored glycogen content in liver ($p < 0.005$) [42].

Melia azadirachta สะเดา

Used in Ethiopian traditional medicine to treat diabetes, chinaberry tree (a.k.a. neem tree) leaf extract elicits diabetic activity through a multitargeted action.

In animal models, it showed an increased insulin-sensitising effect, resulting in blood glucose reduction and improved peripheral glucose disposal [38].

In a recent clinical trial, neem significantly ameliorated hyperglycaemia, endothelial dysfunction, and systemic inflammation, on top of what metformin could do, in subjects with diabetes [39].

Ocimum tenuiflorum กะเพรา

Thai basil, or holy basil, is a very common herb in Thai cuisine. Its medicinal properties have been studied further recently and several studies have proven its effects notably its anti-inflammatory abilities. Some of its compounds can act alone or in combination with other molecules to inhibit inflammatory mechanisms. Thai basil could have beneficial effects on many metabolic disorders when used in conjunction with other plants as reviewed by Jamshidi & Cohen [45].

Ocimum sp. Leaf extract has shown hypoglycaemic effects and therefore can be used as adjunct therapy and drug treatment in mild to moderate Type 2 diabetes [46] [47] [48]. Not only holy basil has effects on blood glucose, but may also prevent formation of atherosclerosis and coronary heart disease in Type 2 diabetic patients [49].

Cinnamomum cassia อบเชย

Cinnamon can significantly lower levels of glucose, triglyceride, low-density lipoprotein cholesterol ("bad cholesterol"), and total cholesterol levels in subjects with type 2 diabetes after 40 days of intake [45]. In a meta-analysis review of 10 randomised clinical trials, Allen *et al.* concluded that the consumption of cinnamon was associated with a statistically significant decrease in levels of fasting plasma glucose, total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels, and an increase in high-density lipoprotein cholesterol ("good cholesterol") levels [46]. A similar review of 16 randomised clinical trials by Deyno *et al.* concluded similarly that cinnamon significantly reduced fasting blood glucose and insulin resistance levels compared to placebo in diabetes and pre-diabetes patients [47].

SUMMARY

Today we live in a world of high technologies and highly processed products. The pharmaceutical industry is often seen as very far from the natural world and very far from traditional medicines that were based on the used of what nature gave us.

However, looking closer into this, the modern western medicine has not rejected nature, it rather has put in place processes for extraction of therapeutic compounds and production on a large scale of synthetic compounds using chemical engineering.

Even today, many common drugs we use commonly or for very advanced treatments originate in the nature around us. Morphine was isolated from the poppy plant (*Papaver somniferum*) two centuries ago and still is used today; the infamous aspirin comes from willow tree bark (*Salix sp.* that gave its name to the active ingredient acetyl salicylic acid). Many antibiotics come from fungi/bacteria (penicillin, tetracycline, erythromycin). Antiparasitic drugs (e.g. avermectin), antimalarials (e.g. quinine, artemisinin), lipid controls agents (e.g. lovastatin), immunosuppressants used in organ transplants (e.g. cyclosporine, rapamycin) and even anticancer drugs (e.g. paclitaxel, irinotecan) come originally from nature [53].

Therawin has selected plants known in traditional medicines from Thailand, China, India to have some effects on diabetes. Using a variety of these plants, Theralin™ combines activity of many natural compounds that provide synergistic effects and acts on several mechanisms underlying diabetes.

Based on the plants Therawin used and on their published scientific evidence, Theralin™ should help with:

- inhibiting the absorption and breakdown of sugars in the intestine to prolong the feeling of satiety (which contributes over time to weight-loss),
- a reduction in the breakdown rate of glucose reserves in the liver between meals (a characteristic of diabetics),
- restoration of pancreatic cells' ability to secrete insulin and control of its rate of secretion, so that it is compatible with the plasma glucose levels,
- increasing receptor activity in the PPAR γ receptor cells in adipose tissue, responsible for the reduction of insulin resistance and an increase in the level of glucose carriers in muscle cells,
- Inhibiting the activity of DPP4 enzyme and increasing the levels of the GLP1 hormone, which will improve the normal physiological function of insulin secretion, an activity sought by most advanced drug treatments.

Theralin™ is a great supplement for:

▪ *People at high risks for diabetes* *Genetic predisposition, diabetes history in family. Highly sedentary lifestyle, diet high in carbohydrates and poor in fibres*	Theralin™' herbs participate in the decrease of chronic inflammation in the pancreas, participate in a lower glycemia and hence help preventing insulin resistance.
▪ *Prediabetic subjects* *Individuals with elevated blood sugar, early glucose intolerance and decreased insulin sensitivity, decreased pancreatic functions.*	Theralin™'s herns can help in restoring insulin sensitivity and glucose tolerance. Theralin™'s herbs participate in protection of insulin-secreting β-cells and in restoring pancreas functions.
▪ *Diabetic patients*	Theralin™'s herbs can be used as an adjuvant care to standard medical treatment of the disease. Through its actions it shall act in synergy with patients' medications and could help, in some patients, reducing the required doses of such medications, hence lowering side effects and improving quality of life*. * effects differ in every patients.

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