THE EFFECT OF IRVINGIA GABONENSIS ON POSTPRANDIAL GLYCEMIC CONTROL AND INSULIN SENSITIVITY IN NON-DIABETIC SUBJECTS

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MASTER OF SCIENCE
IN
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Thesis Title	The Effect of *Irvingia Gabonensis* on Postprandial Glycemic Control and Insulin Sensitivity in Non-diabetic Subjects
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ABSTRACT

Recent epidemiology study has estimated that the prevalence of diabetes is increasing at an extremely higher rate. One of the most well known oriental herbs is *Irvingia Gabonensis*, which has been shown to be efficacious for the treatment and prevention of diabetes in rat (Omoruyi F, Adamson I. Department of Biochemistry, University of Benin, Nigeria). The purpose of this study is to evaluate the influence of *Irvingia Gabonensis* on postprandial plasma glucose level and insulin sensitivity. This study was conducted on 14 subjects, with a crossover design. Subjects were initially screened for non-diabetic status (FBS: < 126 mg/dL). Subjects were randomized to drink either 100ml of *Irvingia Gabonensis* or water 30 minutes prior to 75 grams sucrose solution. Venous blood samples were collected before sucrose ingestion (time point 0) and at 30, 60, 90, 120, and 150 minutes after. After OGTT, participants kept a diary of severity of abdominal and other symptoms score scales. The author found that the *Irvingia Gabonensis* sample group tends to have a lower level of plasma glucose, serum insulin concentrations compared to the controlled group, with significant difference of plasma glocose at 30 (P=0.015), 60 (P=0.022),120 (0.012) and 150 (P<0.01) minutes. The mean difference of the incremental glucose level at each time point also tends to be lower for the *Irvingia Gabonensis* group, with significant difference at 30-min time point

(*P*< 0.01), 60-min time point (P=0.008), 90-min time point (*P*=0.039), 120-min time point (*P*=0.019), 150-min time point (*P*<0.001). To conclude, in non-diabetic subjects, consumption of *Irvingia Gabonensis* aid in postprandial glycemic control during the first 30, 60, 120 and 150 minutes after meal. *Irvingia Gabonensis* does not influence the physiological insulin sensitivity and does not cause significant adverse events.

Keywords: Antihyperglycemic/Insulin sensitivity/*Irvingia Gabonensis*/OGTT/ Pre-diabetes/Non-diabetes

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CHAPTER 1

INTRODUCTION

1.1 Background

Recent epidemiology study has estimated that the prevalence of diabetes is increasing at an extremely higher rate. In 2000, the global diabetes prevalence was 171 million people, and it was estimated in 2006 that the number may rise to approximately 366 million people by the year 2030. However, the actual growing number is much increased, 346 million diabetic patients reported in August 2011 (American Diabetes Association, 2003; Wild, Roglic, Green, Sicree, & King, 2004; World Health Organization, 2006;2011). The national statistic for Thai diabetic patients has also shown a similar pattern of escalation. With diabetes, endocrine, and other metabolic disorders grouped together as a category, the population of this group was 1.58 million people in 2003; the number rose to 2.24 million in 2009 (National Statistical Office, 2003; 2009).

Diabetes and its complications have many negative health impacts. Diabetes is a disease in which the body neither produces or properly utilizes the pancreatic hormone which called "insulin" (Balch, 2006). This results in plasma glucose building up in the bloodstream instead of being taken into and used by the cells, leading to hyperglycemia. If this situation is not properly controlled, diabetes can lead to micro vascular damages, including retinopathy, nephropathy, neuropathy, giving rise to macro vascular complications, including ischemic heart disease, stroke, and peripheral vascular diseases. (World Health Organization, Department of Noncommunicable Disease Surveillance, 1999)

Diabetes does not only have impact against quality of life and physical well being, it also affects patients and their relatives economically. In 2006, the American Diabetes Association, abbreviated as ADA, has made estimation for the national costs of diabetes

merely in the USA in year 2002 to be 132 billion US dollars, and it is projected to increase to 192 billion US dollars in year 2020 (American Diabetes Association, 2003). Preventions and treatments of diabetes are not only available with conventional medicine, but also with traditional medicine. For centuries, local traditional medicines were implemented in countries around the world as natural remedies against illness as well as for tonic and prophylaxis propose. One of the most well known oriental herbs is *Irvingia gabonensis*, which has been shown to be efficacious for the treatment and prevention of diabetes in rat (Omoruyi, F., Adamson, I. Department of Biochemistry, University of Benin, Nigeria)

Clearly, it is imperative for members of the medical research throughout the globe to converge their attention on developing new interventions as well as improving existing treatments that can effectively diagnose diabetes, alleviate its symptoms, and most importantly, prevent the evitable. With *Irvingia gabonensis* as the potential supportive and preventive option for diabetes and pre-diabetes, this study aimed to determine its effect in non-diabetic subjects on levels of plasma glucose, insulin, and the corresponding insulin sensitivity index. In addition, this study determined the correlation of *Irvingia gabonensis* co-ingestion with a meal and the symptoms afterward.

1.2 Research Questions

1.2.1 Primary Question

This study attempted to determine whether co-ingestion of *Irvingia gabonensis* extract by non-diabetic subjects with 75 grams sucrose solution reduces blood glucose fluctuation and improves the whole body physiological insulin sensitivity.

1.2.2 Secondary Question

Since *Irvingia gabonensis* has been shown to induce carbohydrate malabsorption, the study also determined whether co-ingestion of *Irvingia gabonensis* with sucrose solution causes abdominal or other unwanted symptoms.

1.3 Research Objectives

1.3.1 To evaluate the influence of *Irvingia gabonensis* on the blood glucose and whole body physiological insulin sensitivity response to ingestion of sucrose solution by non-diabetic subjects.

1.3.2 To evaluate the severity of abdominal and other symptoms of the subjects after co-ingestion of *Irvingia gabonensis* with sucrose solution.

1.4 Hypothesis

Co-ingestion of *Irvingia gabonensis* extract with 75 grams sucrose solution by non-diabetic subjects can reduce blood glucose fluctuation as well as improving the whole body physiological insulin sensitivity without causing significant abdominal or other symptoms

CHAPTER 2

LITERATURE REVIEW

2.1 Diabetes Mellitus

2.1.1 Overview of Diabetes

Diabetes Mellitus, often shorten as diabetes or DM, is a disease in which the body either does not produce or cannot properly use the pancreatic hormone insulin (Balch, 2006). Glucose, the type of sugar that is most abundant and usable by our body, is the main source of energy for every cell in our body. The levels of glucose in the blood are controlled by insulin, regulating the rate at which glucose is absorbed into the cells.

In normal circumstances, blood glucose will rise after we eat a meal that contains carbohydrate or protein. The increase in blood glucose triggers a release of insulin from cells in the pancreas, known as beta-cells. Insulin in turn stimulates cells throughout the body to allow glucose uptake. This results in the blood glucose levels falling back toward normal. The release of insulin then tapers off until the next time protein or carbohydrates are ingested.

For patients with diabetes, glucose builds up in the bloodstream instead of being taken into and used by the cells, leading to hyperglycemia. If this situation is not properly controlled, diabetes can lead to heart disease, kidney disease, edema, nerve damage, and infections of the mouth, gums, lungs, skin, feet, bladder, and genital areas. Skin sores may develop and fail to heal properly.

Diabetes is a condition primarily defined by the level of hyperglycemia, giving rise to risks of microvascular damage (World Health Organization, Department of Noncommunicable Disease Surveillance, 1999). This includes retinopathy, damage to the eyes, nephropathy, damage to the kidney, and neuropathy, damage to the nervous system. Diabetes is associated with diminished quality of life, as well as reduced life expectancy. It is also associated with significant morbidity due to specific diabetes-related micro

vascular complications and increased risk of macro vascular complications, including ischemic heart disease, stroke, and peripheral vascular diseases.

2.1.2 Global and National Prevalence of Diabetes

Recent epidemiology study has estimated that the prevalence of diabetes is increasing rapidly. The global prevalence of diabetes was 171 million people in the year 2000, and it is projected to increase to 366 million by 2030, doubling within less than 30 years. However, the current number of diabetic patients worldwide has reached 346 million in August 2011, skyrocketing to almost twice the number a decade ago (American Diabetes Association, 2003; Wild et al., 2004; World Health Organization, 2006;2011). Diabetes epidemic is estimated to continuously grow even if the levels of obesity remain constant (Wild et al., 2004). In 2006, the American Diabetes Association, abbreviated as ADA, has made estimation for the national costs of diabetes merely in the USA in year 2002 to be 132 billion US dollars, and it is projected to increase to 192 billion US dollars in year 2020 (American Diabetes Association, 2003).

The national statistical office of Thailand has also reported an increasing trend of diabetes population. In 2003, the total number of Thai population with chronic diseases was about 10.1 million. Among the ten millions, 1.58 million patients were categorized into the group Diabetes/Endocrine system and metabolic disorders (National Statistical Office, 2003). In 2009, the total number of Thai population with chronic diseases was about 10.5 million, which is insignificantly different from six years earlier. However, the number of patients that were categorized into the group Diabetes/Endocrine system and metabolic disorders was 2.24 million people, which is approximately 42 percent larger than the previous data (National Statistical Office, 2009).

Table 2.1 The 2003 and 2009 Statistic of Thai Population with Chronic Diseases

Group of Chronic Diseases	Year 2003	Year 2009
Total	**10,170,660**	**10,519,386**
Diabetes/Endocrine system and metabolic disorders	1,578,446	2,236,593
Cardiovascular diseases	2,072,358	4,044,260
Musculo-skeletal disorders	1,742,736	1,375,210
Diseases of the digestive system	1,015,666	397,514
Diseases of the respiratory system	923,381	1,721,809
Diseases of the nervous system and mental disorder	602,846	453,665
Diseases of urinary system	210,847	303,596
Infectious diseases	86,241	81,903

Source National Statistical Office (2003)
National Statistical Office (2009)

The latter figures implicate the correlated global trend of increasing diabetes prevalence. The number of people around the world suffering from diabetes has clearly skyrocketed in the last few decades, claiming millions of lives and severely taxing the ability of health care systems to deal with the epidemic. It is therefore imperative for members of the medical research throughout the globe to converge their attention on developing new interventions as well as improving existing treatments that can effectively diagnose diabetes, alleviate its symptoms, and most importantly, prevent the evitable.

2.1.3 Pathophysiology and Classification of Diabetes (American Diabetes Association, 2008)

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin, action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels.

Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the beta cells of the pancreas with consequent insulin deficiency to abnormalities that result in resistance to insulin action. The basis of the abnormalities in carbohydrate, fat, and protein metabolism in diabetes is deficient action of insulin on target tissues. Deficient insulin action results from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action. Impairment of insulin secretion and defects in insulin action frequently coexist in the same patient, and it is often unclear which abnormality, if either alone, is the primary cause of the hyperglycemia.

The vast majority of cases of diabetes fall into two broad etiopathogenetic categories, with other categories of abnormal glucose regulation often assigned according to the circumstances present at the time of diagnosis. Many diabetic individuals do not easily fit into a single class.(American Diabetes Association, 2008)

2.1.3.1 Type 1 Diabetes

Type 1diabetes affects 5 to 10 percent of people with diabetes and usually starts at an early age. It is referred to by several names, including insulin-dependent diabetes mellitus (IDDM), DM type 1, and juvenile diabetes. This type of diabetes results from the body's failure to produce insulin, thus constantly requiring exogenous insulin administration. It is characterized by loss of the insulin-producing beta cells of the islets of Langerhans in the pancreas, leading to insulin deficiency. This type of diabetes can be further classified as either immune-mediated or idiopathic. The majority of type 1 diabetes is of the immune-mediated nature, where beta cells are attacked by self immuneT-cell (autoimmune) (Rother, 2007). There is no known preventive measure against type 1 diabetes. Most affected people are otherwise healthy and of a healthy weight when onset occurs. Sensitivity and responsiveness to insulin are usually normal, especially in the early stages. Type 1 diabetes can affect children or adults, but was

traditionally termed juvenile because it represents a majority of the diabetes cases in children.

2.1.3.2 Type 2 Diabetes

Type 2 diabetes, by far the most common form of diabetes, affects 90 to 95 percent of diabetes sufferers. It is formerly referred to as non-insulin-dependent diabetes mellitus (NIDDM) and adult-onset diabetes. In type 2 diabetes, the pancreas does produce insulin in small quantities, but not enough to fuel the cells. The cells may also become resistant to the effects of what little insulin there remains in the bloodstream. This type of diabetes is therefore characterized by insulin resistance which may be combined with relatively reduced insulin secretion. The defective responsiveness of body tissues to insulin may involve the insulin receptor. In the early stage of type 2 diabetes, the predominant abnormality is reduced insulin sensitivity. At this stage, hyperglycemia can be reversed by a variety of measures and medications that improve insulin sensitivity or reduce the production of glucose by the liver.

2.1.3.3 Gestational Diabetes

Gestational diabetes mellitus, GDM for short, is when pregnant women, who have never had diabetes before, have a high blood sugar level during pregnancy. GDM resembles type 2 diabetes in several respects, involving a combination of relatively inadequate insulin secretion and responsiveness. Hormonal changes during pregnancy can affect the body's resistance to insulin. It occurs in about 2-5% of all pregnancies and may improve or disappear after delivery, but it seems to be a sign that the woman is more likely to develop type 2 diabetes in later life. Gestational diabetes is fully treatable, though it requires careful medical supervision throughout the pregnancy.

Although it may be transient, untreated gestational diabetes can damage the health of the fetus or mother. Risks to the baby include macrosomia (high birth weight), congenital cardiac and central nervous system anomalies, and skeletal muscle malformations. Increased fetal insulin may inhibit fetal surfactant destruction. In severe cases, perinatal death may occur. Labor induction may be indicated with decreased placental function.

The American Diabetes Association has defined GDM as "type 3 diabetes" (American Diabetes Association, 2005).

2.1.4 Diabetes Signs and Symptoms

The classical symptoms of diabetes are frequent urination (polyuria), increased thirst (polydipsia), and increased hunger (polyphagia) (Cooke & Plotnick, 2008). Symptoms may develop rapidly in type 1, perhaps weeks or months. On the other hand, symptoms usually develop much more slowly and may be subtle or absent for type 2 diabetes.

For the eyes, prolonged high blood sugar will lead to excess glucose absorption, resulting in changes in shape of the lenses, causing changes in vision. Glucose level management has to be sustained, and the lens would usually return to its original shape. Blurred vision is a common complaint leading to a diabetes diagnosis.

Diabetic Ketoacidosis, shortly called DKA, may also be present at a later state. It is a condition of metabolic dysregulation characterized by the smell of acetone; a rapid, deep breathing known as Kussmaul Breathing, nausea, vomiting, and abdominal pain (Kussmaul, edtior, 1874).

Hyperosmolar nonketotic state is similar to the latter condition except it is not resulted from excess ketone bodies. This condition is more common in type 2 diabetes and is mainly the result of dehydration. Diabetes patients often drink extreme amount of sugar-containing drinks, leading to a vicious cycle in regard to the loss of water (Cirasino, Thiella, Invernizzi, Silvani, & Ragaini, 1992).

A number of skin rashes can occur in diabetes that are collectively known as diabetic dermadromes(James & Berger, editors, 2006).

2.1.5 Current Criteria for the Diagnosis of Diabetes

Previously, the Department of Noncommunicable Disease Surveillance, World Health Organization, had provided the definition and diagnosis criteria of diabetes with two tests; the fasting plasma glucose, and 2-h glucose test. In 2010, the American Diabetes Association Standards of Medical Care in Diabetes added the glycohemoglobin $\geq$ 6.5% ($\geq$ 48 mmol/mol) as another criterion for the diagnosis of diabetes. In short, diabetes mellitus is characterized by recurrent or persistent hyperglycemia. It is diagnosed by demonstrating any one of the conditions in the following table.

Table 2.2 Current Criteria for the Diagnosis of Diabetes– 2010

Type of Blood Test	Level of Plasma Concentration for Diabetes
Glycohemoglobin (HbA1C)	≥ 6.5% (48 mmol/mol)
Fasting Blood Sugar (FBS, FPG)	≥ 126 mg/dl (7.0 mmol/l)
2-h or Random Plasma Glucose	≥ 200 mg/dl (11.1 mmol/l)

Source "Executive summary: Standards of medical care in diabetes" (2010)

2.1.6 Medications used in Diabetes

Type 2 diabetes may be managed with any number of different drugs. The following table is a summary of the major medications currently used for diabetes management together with how they act in the body, generic and brand names, and general description.

2.1.6.1 Oral Antidiabetic Agents

Orally administered drugs available for the treatment of type 2 diabetes include the sulfonylureas, the biguanide metformin, the alpha-glucosidase inhibitor, and the thiazolidinedione. These agents reduce blood glucose levels by different mechanism.

1. Sulfonylureas

Sulfonylureas (SFU) are the first oral agents available for the treatment of type 2 diabetic subjects. Sulfonylureas promote insulin secretion through direct stimulation of pancreatic beta cells. They bind to ATP-sensitive potassium channels and inhibit potassium ion efflux. The resulting depolarization allows influx of calcium ions through the voltage-dependent calcium channels. The release of insulin is triggered by the rise of intracytosolic calcium ion concentration. Secondary failure of sulfonylureas-induced insulin secretion results from beta cell "exhaustion", which occurs in approximately 10% of patients per year. After 10 years of treatment by sulfonylureas, approximately 50% of the treated patients become non-responder (Oiknine & Mooradian, 2003).

All sulfonylureas are able to augment insulin secretion in patients with type 2 diabetes who still have pancreatic insulin reserve. These drugs have different

durations of action, dose responses, and side effects. Sulfonylureas can reduce the level of fasting plasma glucose by 20-30%. They have a substantial primary and secondary failure rate. Potential side effects of sulfonylureas include hypoglycemia, weight gain, and hyperinsulinemia. Thus, it is relatively uncommon for patients treated with sulfonylureas alone to achieve normoglycemia. Sulfonylureas may be used in combination with other oral agents or insulin. Although this approach has been shown to decrease insulin requirements in some patients with type 2 diabetes, it is not effective in all patients. In addition, these patients may encounter episodes of hypoglycemia (Lipkin, 1999).

2. Meglitinides

These agents are non-sulfonylurea secretagogues with a sulfonylurea-like mechanism of action. They target a different binding site on pancreatic beta cells, leading to a similar cascade of events triggering insulin release. Repaglinide, a benzoic acid derivative, and the new agent, nateglinide, a phenylalanine derivative, are examples of drugs belonging to this class of agents. Their pharmacokinetic profile is favorable in terms of targeting postprandial hyperglycemia.

Repaglinide is completely metabolized by the liver and eliminated mostly by biliary route (90%). The drug elimination kinetics is widely variable; its half-life ranges between 0.5 hours and 8 hours. In elderly patients with type 2 diabetes mellitus who have reduced creatinine clearance, the mean diurnal plasma concentration was found to be significantly higher than healthy controls. Similar results were noticed in patients with moderate to severe liver disease. Nateglinide should also be used cautiously in the context of renal and/or hepatic impairment. Studies have proved repaglinide as efficacious as sulfonylureas. Nateglinide, however, appears to be less potent than sulfonylureas. Another drawback in using these agents is the frequent pre-meal dosing that may affect compliance. Although it was hoped that weight gain and hypoglycemia would occur less often with Meglitinides than with sulfonylureas, a recent clinical trial found no major clinical advantage when repaglinide was compared to glipizide(Lipkin, 1999).

3. Biguanides

Metformin is the biguanide that is most prescribed worldwide. It is much safer than earlier biguanides, phenformin and buformin. The latter agents were withdrawn from the market because of their tendency to cause lactic acidosis. Its principal action is to reduce hepatic gluconeogenesis. Excessive hepatic glucose production is then diminished at any given level of plasma insulin. To a lesser degree, possibly an indirect effect, metformin increases insulin mediated glucose uptake and utilization in peripheral tissues, especially in the muscle. Metformin is therefore an antihyperglycemic agent preferred in obese patients with insulin resistance. Metformin is not metabolized and mostly renally excreted (90%) in 12 hours. Its bioavailability is approximately 50 to 60 percent, being absorbed mainly from the small intestine. The estimated plasma half-life is about 1.5 to 4.9 hours. Metformin is found to rarely bind to plasma proteins. It is beneficial at a low dose of 500 mg per day with meals, demonstrating a progressive response to doses up to 2000 mg per day. Although metformin is approved for up to 2550 mg per day, little additional benefit is seen beyond 2000 mg dose. It is not associated with weight gain and reduced adiposity. Metformin also has a modest antihypertensive and antihyperlipidemic effect, with slight increase in HDL cholesterols and decrease in triglycerides and LDL cholesterols (Lipkin, 1999).

As monotherapy, it does not cause hypoglycemia. It can be used as a single agent with efficacy equivalent to that of sulfonylurea; otherwise both agents in combination are also feasible. This combination has the potential of achieving normoglycemia in patients with type 2 diabetes without concomitant weight gain and hyperinsulinemia. Metformin may also be used with alpha-glucosidase inhibitor or insulin. Of the newer drugs, studies indicate that metformin is best for normalizing abnormal blood lipids. Contraindications to the use of metformin include kidney disease, having serum creatinine level greater than 130 micromol/l in men and 120 micromol/l in women, diabetic ketoacidosis, and pregnancy (Lipkin, 1999).

4. Thiazolidinediones

This class of agents is relatively new. It is the most expensive class of antidiabetic agents. Troglitazone, the first compound in this class, was withdrawn from the market because of its association with unpredictable fulminant hepatic failure. The

two currently available agents, rosiglitazone and pioglitazone, do not appear to have the same tendency to cause hepatotoxicity.

Thiazolidinediones enhance glucose uptake and utilization in peripheral tissues, mainly skeletal muscle. Thiazolidinediones bind to the peroxisomal proliferator-activated receptor (PPAR-gamma). The nuclear receptor most highly expressed not only in adipose tissue, but also found in skeletal muscle, liver, intestine, kidney, vascular smooth muscle, heart, and macrophages. Once activated, PPAR-gamma receptor binds to DNA, leading to transcriptional modulation of genes involved in carbohydrate and lipid metabolism. Thiazolidinediones decrease insulin resistance in peripheral tissues with only a minor effect on hepatic glucose production at high doses. Given the abundance of PPAR-gamma receptors in adipocytes compared to myocytes, the predominant action of thiazolidinediones on skeletal muscle may be through an indirect interaction between fat and muscle cells.

Thiazolidinediones do not cause hypoglycemia when used alone. Rosiglitazone and pioglitazone have a half-life ranging between 3 to 7 hours. Some active metabolites of pioglitazone have longer half-lives. These agents are 99 percent protein bound. Rosiglitazone and pioglitazone have minimal drug-drug interaction. While pioglitazone partially induce the cytochrome P450 system, metabolized through the CYP2C8 isoenzyme and CYP3A1, rosiglitazone is metabolized through the CYP2C8 isoenzyme only and does not induce the cytochrome P450 system. Thiazolidinediones are hepatically metabolized and eliminated by biliary route. The dose of glitazones does not need to be adjusted for renal insufficiency. But in the context of hepatic failure, thiazolidinediones must be discontinued. Nevertheless, rosiglitazone and pioglitazone have not demonstrated an increased rate of liver enzyme abnormality so far. Based on the troglitazone experience, the current recommendation is still to monitor liver enzymes at baseline every other month in the first year and periodically afterward.

Thiazolidinediones also have non-hypoglycemic effect. Both rosiglitazone and pioglitazone slightly raise HDL cholesterol levels. LDL cholesterol levels are increased with both agents although more so with rosiglitazone. Pioglitazone, but not rosiglitazone, may have a triglyceride lowering effect possibly because of its additional PPAR-gamma activity. Thiazolidinediones also slightly reduce blood pressure, enhance

fibrinolysis, improve endothelial function, and decrease *in vitro* vascular inflammation (Lipkin, 1999).

5. Alpha-Glucosidase Inhibitors

There are three agents in this category that are currently marketed worldwide. These include acarbose, miglitol, and voglibose. These agents primarily target postprandial hyperglycemia. Postprandial hyperglycemia has been linked with cardiovascular mortality.

Alpha-glucosidase inhibitors have a unique mechanism of action. These agents competitively inhibit alpha-glucosidases, the brush border enzymes of the proximal small intestinal epithelium. This reversible inhibition delays hydrolysis of polysaccharides into absorbable monosaccharides, such as glucose. Carbohydrate absorption occurs over a greater portion of the small intestine, blunting postprandial glucose excursions.

Hypoglycemia may occur when alpha-glucosidase inhibitors are used in combination therapy with either insulin or sulfonylureas. In that context, glucose rather than sucrose or complex carbohydrate should be used. Glucose is readily absorbed and will promptly correct hypoglycemia.

Alpha-glucosidase inhibitors are safe and may be suitable agents in the elderly diabetic patients, either as monotherapy or in combination therapy. The need for multiple pre-meal dosing, gastrointestinal side effects, and cost may however limit their use.(Lipkin, 1999)

In general, when proper glycemic control is not achieved despite diet, exercise, and the use of other oral antidiabetic agents, insulin therapy is often necessary.

Current clinical uses of diabetes medication include all of the mentioned antidiabetic drugs, which cause certain adverse drug reactions. Some of them are of high costs, leaving many patients with suboptimal treatments. In present, remedies of natural source illustrate considerable potentials, claiming to be capable of reducing elevated blood glucose levels. These remedies, including *M. alba* L., may be developed in search of a better anti-diabetic agent with cost-effectiveness, efficacy, and safety.

Table 2.3 Oral Medications for Type 2 Diabetes

Action in the Body	Generic Name	Brand Name(s)	Descriptions
Sulfonylureas			
Stimulates beta cells to release more insulin	Chlropropamide	Diabinese	Take one or two times daily before meals. First-generation drug
	Glipizide	Glucotrol	Second-generation drug. Used in smaller doses than first-generation agents.
	Glyburide	DiaBeta Micronase Glynase	Second-generation drug. Smaller doses.
	Glimepiride	Amaryl	Second-generation drug. Smaller doses.
Meglitinides			
Stimulate the pancreas to release more insulin	Repaglinide	Prandin	Taken before each of three meals.
Nateglinides			
Works similarly to sulfonylureas	Nateglinide	Starlix	Taken before each of three meals.
Biguanides			
Sensitizes the body to insulin already present	Metformin	Glucophage	Taken two times daily with food for best results.
	Metformin Extended Release	Glucophage XR	
	Metformin with Glyburide	Glucovance	

Table 2.3 (continued)

Action in the Body	Generic Name	Brand Name(s)	Descriptions
Thiazolidinediones (Glitazones)			
Help insulin work better in muscle and fat and lowers insulin resistance	Rosiglitazone Pioglitazone	Avandia Actos	Taken once or twice daily with food. Very rare but serious side effects on the liver are possible
Alpha-Glucosidase Inhibitors			
Slows or blocks breakdown of starches and sugars; action slows rise in blood sugar after eating	Acarbose Miglitol Voglibose	Precose Glyset Basen	Should be taken with first bite of meals.

Source Balch (2006)

Type 1 diabetes is managed with injections for the hormone insulin, as well as with close attention to diet and other lifestyle factors. Not all insulins are the same, however, and it may take some trial and error to find the one or ones that are right for any given individual. The principal differences are related to the speed with which they take effect, and the period of time they remain active in the body. The following table shows the major types of insulin that are commonly available and used in the present.

Table 2.4 Insulin Preparations for Type 1 Diabetes

Insulin Type	Onset of Action	Peak of Action	Duration of Action
Long-Acting Insulin			
Humalog (Lispro)	15 minutes	30-90 minutes	3-5 hours
NovoLog (Aspart)	15 minutes	40-50 minutes	3-5 hours
Short-Acting Insulin (Regular)			
Humulin R	30-60 minutes	50-120 minutes	5-8 hours
Novolin R	30-60 minutes	50-120 minutes	5-8 hours
Intermediate-Acting Insulin (NPH)			
Humulin L	1-2.5 hours	7-15 hours	18-24 hours
Humulin N	1-3 hours	8 hours	20 hours
Novolin N	1-3 hours	8 hours	20 hours
Intermediate- and Short-Acting Insulin Mixtures			
Humulin 50/50 Humulin 70/30 Humulin Mix 75/25 Humulin Mix 50/50 Novolin 70/30 Novolog Mix 70/30	The onset, peak, and duration of action of these mixtures reflect a composite of the intermediate- and short- or rapid-acting components, with one peak of action.		
Long-Acting Insulin			
Ultralente	4-8 hours	8-12 hours	36 hours
Lantus (Glargine)	1 hour	None	24 hours

Source Balch (2006)

2.1.7 Medicinal Herbs with Anti-diabetic Activities

For many centuries, local traditional medicines were implemented in countries around the world as natural remedies against illness. After the development of the modern conventional medicine, recent uses of these traditional herbs still continue for several reasons, including the local belief of efficacy and, more importantly, safety as opposed to

the modern drugs that inevitably come along with adverse drug reactions that may occur after prolonged usage.

Therapeutic properties of herbal remedies are versatile. One of them includes anti-diabetes, which involve the use of several plants with multiple parts. Other than *M. alba*L., which is the plant of this study's concern, the following table displays a list of plants that have been used for its anti-diabetic properties.

Table 2.5 List of plants with Anti-Diabetic Activity

Botanical name	Family	Parts used	Mechanism of action	Chemical constituents
*Abiespindrow*Royle	Pinaceae	Entire plant	Insulin secretagogue activity	Volatile oil
Abromaaugusta Linn	Sterculiaceae	Roots & Leaves	Lowering blood sugar	Fixed oil, Alkaloid
Acacia arabica Wild	Leguminosae	Seed	Initiates release of insulin	Arabin
Achyranthusaspera L		Entire plant	Decreases blood sugar	
Agrimony eupatoria L.	Rosaceae	Leaves	Insulin releasing & insulin like activity	
Ajaugaiva Wall. ex. Benth	Labiatae	Entire plant	Decreases plasma glucose level	
Allium sativum Linn.	Liliaceae	Roots	Antihyperglycemic and antinociceptive effect	Volatile oil, Allin, Allicin
Allium cepa Linn.	Liliaceae	Bulb	Stimulating effects on glucose utilization and antioxidant enzyme	Protein, carbohydrate, vitamin A, B, C, Allylpropyldisulphide

Table 2.5 (continued)

Botanical name	Family	Parts used	Mechanism of action	Chemical constituents
*Aloe veraTourn.*ex. Linn.	Liliaceae	Entire plant		Aloin glycoside
Aloe barbadensis Miller	Liliaceae	Leaves	Stimulating synthesis and/or release of insulin	Barbaloin, isobarbaloin, resin
Amaranthusspinosus Linn.	Amaranthaceae	Stem		
Anacardiumoccidentale Linn	Anacardiaceae	Entire plant		Flavonols, terpenoid, caumarin, phenolic compound,essential oil
Andrographispaniculata Nees	Acanthaceae	Entire plant	Increases glucose metabolism	Diterpenoid lactone andrographoloid
Annonasquamosa	Annonaceae	Leaves	Hypoglycemic and anti-hyperglycemic activities	Acetogenins-squamosin B, squamosamide, reticulatain-2,isosquamosin
Artemisia pallens Wall	Compositae	Aerial parts	Leaf-extract, increased plasma insulin level, hypoglycemic, increases peripheral glucose utilization or inhibits glucose reabsorption	Essential oil, davanone

Table 2.5 (continued)

Botanical name	Family	Parts used	Mechanism of action	Chemical constituents
Averrhoabilimbi	Oxalidaceae	Leaves	Increases serum insulin level	
*Azadirachtaindica*A.juss.	Meliaceae	Leaves	Glycogenolytic effect due to epinephrine action was blocked	Nimbidin, nimbin, nimbidol, nimbosterol
Beta vulgaris Linn	Chenopodiaceae		Reduces blood glucose level by regeneration of beta cells	
Bidenspilosa	compositae	Aerial parts		Polyacetylenicglucoside
Bixaorellana L.	Bixaceae	Entire plant	Increases plasma insulin concentration & increases insulin binding on insulin receptor	Oleo-resin
Boerhaaviadiffusa L.	Nyctaginaceae	Leaves & Entire plant	Increases in hexokinase activity, decreases in glucose-6-phosphatase	Alkaloid punarnavaine, punarnavoside
Brassica juncea L.	Cruciferae		Food adjuvants for diabetic patients	Isothiocyanate glycoside singrin, protein, fixed oil
Caesalpiniabonducella Flem.	Leguminose	Seed kernels	Free radical scavenging	Fatty oil
Camellia sinensis	Theaceae	Leaves	Increases insulin secretion	Polyphenolic constituents (EGCG)

Table 2.5 (continued)

Botanical name	Family	Parts used	Mechanism of action	Chemical constituents
*Capparisdeciduas*Edgew	Capparidaceae	Powder	Hypoglycemic, antioxidant, hypolipidaemic	
Capsicum frutescens Linn.	Solanaceae		Increases insulin secretion & reduction of insulin binding on insulin receptor	
Carumcarvi Linn.	Umbelliferae	Fruits		Volatile oil, resin, carvone, fixed oil
Cassia alata	Caesalpiniaceae	Leaves		
Cassia auriculata	Caesalpiniaceae	Flower	Increases utilization of glucose through increase glycolysis	
*Catharanthusroseus*G.Don	Apocynaceae	Leaves, twig & flower	Increases metabolisation of glucose	Indole alkaloid, vincristine vinblastin
Cinnamomumzeylanicum Nees	Lauraceae	Bark	Elevation in plasma insulin	Volatile oil, tannin, mannitol, calcium oxalate
*Clausenaanisata*Burm.f.	Rutaceae	Roots	Stimulates secretion of insulin	
Coriandrumsativum Linn.	Umbelliferae	Seed		Volatile oil, fixed oil, protein
Cosciniumfenestratum Calebr	Menispermaceae	Stem	Increases enzymatic antioxidants	Barberine , glycoside, saponin
*Croton cajucara*Benth	Euphorbiaceae	Bark		Fixed oil
Cryptolepissanguinolenta R.	Asclepidaceae	Entire plant	Increases glucose uptake by 3T3-L1 cells	Cryptolepine

Table 2.5 (continued)

Botanical name	Family	Parts used	Mechanism of action	Chemical constituents
Eclipta alba Linn.	Compositae	Leaves	Decreases activity of glucose-6-phosphatase & fructose-1-6,bisphasphatase	Ecliptin alkaloid
Embellicaofficinalis Gaertn.	Euphorbiaceae	Fruits	Reduces 5-hydroxymethylfurfural, creatinine albumin level	Vitamin C, tannin
Enicostemmalittorale Blume	Gentianaceae	Entire plant	Decreases glycosylated Hb& glucose 6 phosphatase	Swertiamarine glycoside
Eugenia jambolana Lam.	Myrtaceae	Seed, fruit , leaves, kernel	Lowers plasma glucose level	
*Eucalyptus globulus*Labill.	Myrtaceae	Leaves	Increases insulin secretion from clonal pancreatic beta line (BRIN-BD 11)	Essential oil , cineol
Euphrasiaofficinale	Scrophulariaceae	Leaves		
Ficusreligiosa Linn.	Moraceae	Entire plant	Initiating release of insulin	Tannin
Ficusbengalensis Linn.	Moraceae	Bark	Rising serum insulin	Tannin
Ficuscarica	Moraceae	Leaves		
Gymnemamontanum Hook f.	Asclepiadaceae	Leaves	Antioxidant &antiperoxidative	
Gymnemasylvestre R.	Asclepiadaceae	Leaves	Lowers plasma glucose level	Gymnemic acid, quercital

Table 2.5 (continued)

Botanical name	Family	Parts used	Mechanism of action	Chemical constituents
*Gentianaolivier*Griseb.	Gentianaceae	Flowers	Lowers plasma glucose level	Iso-orientin C-glycoside
Glycerrhizaglabra Linn.	Leguminosae	Root	Lowers plasma glucose level	Triterpenoid,saponin, glycerrhizin
Gynuraprocumbens	Compositae	Leaves	Lowers plasma glucose level	
Hibiscus rosasinensis Linn.	Malvaceae	Entire plant	Stimulates insulin secretion from beta cells	Vitamin B, C, fat
Helicteresisora Linn.	Sterculiaceae	Root	Decreases plasma triglyceride level & insulin sensitizing activity	Saponin, tannin, lignin
Hordeumvulgare	Graminaeae			
*Hoveniadulcis*Thunb	Rhamnaceae	Entire plant		Flavonoids
*Ipomoea aquatica*Forsk.	Convolvulaceae	Leaves	Reduces fasting blood sugar level & serum glucose level	Carotene
Ipomoea batata Linn.	Convolvulaceae	Tubers	Reduces insulin resistance & blood glucose level	
Juniperuscommunis Linn.	Pinaceae	Fruits	Increases peripheral glucose consumption & induce insulin secretion	
Lupinusalbus Linn.	Fabaceae	Seed	Lowering serum glucose level	Alkaloid, fatty oil, asparagines
Luffaaegyptiaca Mill.	Cucurbitaceae	Seed	Lactigogue activity	Fatty oil

Table 2.5 (continued)

Botanical name	Family	Parts used	Mechanism of action	Chemical constituents
Leucaslavandulaefolia Rees	Labiatae	Entire plant	Reduces blood glucose level	
Lagerstronemiaspeciosa	Lythraceae	Leaves		
Lepidiumsativum	Cruciferae	Seeds		
Mangiferaindica Linn.	Anacardiaceae	Leaves	Reduction of intestinal absorption of glucose	Mangiferin
Myrtuscommunis L.	Myrtaceae	Leaves	Lowering blood glucose level	Volatile oil, mirtiioleum
Memecylonumbellatum Burm	Melastomataceae	Leaves	Lowering serum glucose	
Momordicacymbalania Fenzl ex naud	Cucurbitaceae	Fruit powder	Reduces blood glucose level	
Mucunapruriens L.	Leguminosae	Seed	Reduces blood glucose level	
Musa sapientum Linn.	Musaceae	Flower	Reduces blood glucose & glycosylated Hb	
Momordicacharantia Linn.	Cucurbitaceae	Fruit	Reduces blood glucose level	Momordicine alkaloid, ascorbic acid
M. indica L.	Moraceae	Leaves	Increases glucose uptake	
Murrayakoeingii (L) spreng.	Rutaceae	Leaves	Increases glycogenesis , decrease glycogenolysis& gluconeogenesis	
*Nelumbonucifera*Gaertn.	Nymphaeaceae	Rhizome	Reduces blood sugar level	Nuciferin, nornuciferin

Table 2.5 (continued)

Botanical name	Family	Parts used	Mechanism of action	Chemical constituents
Ocimum sanctum Linn.	Labiatae	Leaves	Lowering blood sugar level	Volatile oil, phenol, aldehyde, fixed oil, alkaloid, tannin, ascorbic acid
Oleaeuropia Linn.	Oleaceae	Leaves	Potentiation of glucose , induced insulin released , & increase peripheral uptake of glucose	Oleuropeoside
Opuntiaficus-indica Mill	Cactaceae	Stem		
Pandanusodorus Linn.	Pandanaceae	Root	Decreases plasma glucose level	Essential oil
*Panaxginseng*Mey.	Araliaceae	Root & entire plant	Lowering blood sugar level	Glycans, panaxans I,J,K & L
Punicagranatum Linn	Punicaceae	Seed	Reduces blood sugar level	Vitamin C, protein, tannin, gallic acid, pelletierine
Picrorrhizakurroa Royle ex. Benth	Scrophulariaceae	Entire plant	Decreases serum glucose	Picrorrhizin, kutkin
Phyllanthusamarus	Euphorbiaceae	Entire plant	Decreases blood glucose level	Alkaloids
Phaseolus vulgaris	Papilionaceae	Pod, seed, whole plant	Hypoglycemic, hypolipidemic, inhibit alpha amylase activity, antioxidant.	
Salaciaoblonga	Celastraceae	Root	Inhibition of alpha glucosidase activity	

Table 2.5 (continued)

Botanical name	Family	Parts used	Mechanism of action	Chemical constituents
Salaciareticulata Wight.	Celastraceae	Stem & root	Inhibition of alpha glucosidase activity	
*Swertiachirayata*Roxb.ex. Flem	Gentianaceae	Entire plant	Stimulates insulin release from islets	Zanthonemangiferi, gentianine, swerchirin
Syzygiumcumini Linn	Myrtaceae	Seed	Decreases blood glucose level	
Scopariadulcis Linn.	Scrophulariaceae	Leaves	Decreases glycosylated Hb& Increases total Hb, Insulin-secretagogue activity	
Trigonellafoenumgraceum	Leguminosae	Seed	Decreases blood glucose concentration	Protein, fat, volatile oil, fixed oil, carbohydrate
Tribulusterrestris Linn.	Zygophyllaceae	Saponin	Decreases serum glucose	Harmine
Tinosporacrispa Linn.	Menispermaceae	Stem	Anti-hyperglycemic, stimulates insulin release from islets	
Tinosporacardifolia Wild.	Menispermaceae	Root	Decreases blood glucose & brain lipid	Berberine, starch
Tamarindusindica Linn.	Caesalpimiaceae	Seed		
Teramnuslabialis (Roxb) Benth	Fabaceae	Aerial parts		Caumarin–fraxidin
Urtifcadioica Linn.	Urticaceae	Leaves	Increases insulin secretion	Fatty oil

Table 2.5 (continued)

Botanical name	Family	Parts used	Mechanism of action	Chemical constituents
Viscum album Linn.	Loranthaceae	Entire plant	Alpha glucosidase inhibitor	
Vincarosea	Apocynaceae	Leaves	Beta cell rejuvenation, regeneration, & stimulation	Vincristine, vinblastine
*Withaniasomnifera*Dunal	Solanaceae	Root	Decrease blood sugar level	Withanine, somnine, withaferine, withanolides
Xanthium strumarium	Compositae	Fruits	Increases glucose utilization	Phenolic compound,caffeic acid
Zingiberofficinale Roscoe	Zingiberaceae	Rhizome	Increases insulin level & decrease fasting glucose level	Sesquiterpene
Zizyphus sativa Gaertn	Rhamnaceae	Leaves	Dose dependent reduction in blood glucose level	Tannin

Source Mishra, Rao, Ojha, Vijayakumar & Verma, 2010

2.2 Pre-Diabetes

2.2.1 Overview of Pre-Diabetes

Before people develop type 2 diabetes, they typically have to go through the phase of being "Pre-diabetic," the condition that the levels of fasting plasma glucose is below the overt excess threshold which is used to diagnose diabetes, yet significantly higher than the normoglycemia baseline. There were 41 million people in the United States who have pre-diabetes in 2006 (American Diabetes Association, 2006). As of 2011, the number has dramatically risen to 79 million people (American Diabetes Association, 2011b), practically double within merely 5 years. Recent research has shown that some long-term damage to the body, especially the heart and the circulatory system, may have already been done during the pre-diabetic period. Research has also shown that if actions are taken to manage the blood glucose level during pre-diabetes, it is possible to delay or even prevent type 2 diabetes from ever developing. People with pre-diabetes can expect to benefit from much of the same advice good for nutrition and physical activity.

Impaired glucose tolerance, abbreviated as IGT, is a degree of hyperglycemia which may precede type 2 diabetes. IGT is formerly known as "Borderline Diabetes." Another similar terminology is IFG, standing for impaired fasting glucose. Both conditions are considered a pre-diabetic state, associated with insulin resistance and increased risk of cardiovascular pathology, although IFG is of lesser risk than IGT (Nicholas, Hillier, & Brown, 2007).

2.2.2 Criteria for the Diagnosis of Pre-Diabetes

While diabetes and pre-diabetes occur in people of all ages and races, some groups have a higher risk for developing the disease than others. Diabetes is more common in African Americans, Latinos, Native Americans, and Asian Americans/Pacific Islanders, as well as the aged population. This means they are also at increased risk for developing pre-diabetes.

There are three different tests that can be used to determine whether a person has pre-diabetes (American Diabetes Association, 2011a).

2.2.2.1 *Glycated Hemoglobin*: Medical communities of different areas around the world have several synonyms for this term, including hemoglobin A1C,

glycohemoglobin, HbA1C, A1C, or Hb1c. The measurement primarily aids in identifying the average plasma glucose concentration over prolonged periods of time.

2.2.2.2 *Fasting Plasma Glucose*: Fasting plasma glucose is abbreviated as FPG and is also called Fasting Blood Sugar (FBS) in some countries, including Thailand. Overt value of FPG reflects the condition of impaired fasting glucose (IFG).

2.2.2.3 *Oral Glucose Tolerance Test (OGTT)*: This is a medical test in which glucose is given, then blood samples are collected continuously 2 hours afterward to determine how quickly the glucose levels return to normal. Overt value of plasma glucose after OGTT reflects the condition of impaired glucose tolerance (IGT).

Table 2.6 Current Criteria for the Diagnosis of Pre-Diabetes - 2010

Type of Blood Test	Level of Plasma Concentration for Pre-Diabetes
Glycohemoglobin (HbA1C)	≥ 5.7% (39 mmol/mol)
Fasting Blood Sugar (FBS, FPG)	≥ 100 mg/dl (5.6 mmol/l)
2-h or Random Plasma Glucose	≥ 140 mg/dl (7.8 mmol/l)

Source "Executive summary: Standards of medical care in diabetes" (2010)

2.2.3 Prophylaxis of Diabetes

The plasma glucose levels of a person, as well as his or her insulin demand, will rise more rapidly after having a meal with high glycemic load. The high level of plasma glucose and excessive insulin secretion had been shown to contribute to the loss of insulin-secreting function of the pancreatic beta-cells that leads to irreversible diabetes (Willett, Manson, & Liu, 2002). Several large prospective studies have shown that high dietary glycemic loads are associated with an increased risk of type 2 diabetes development (Gross, Li, Ford, & Liu, 2004; Krishnan et al., 2007; Salmerón, Ascherio, et al., 1997; Salmerón, Manson, et al., 1997; Schulze et al., 2004; Villegas et al., 2007).

2.3 *Irvingia Gabonensis*

2.3.1 Scientific Classification and Botanical Nomenclature

Irvingia is a genus of African and Southeast Asiantrees in the family Irvingiaceae, sometimes known by the common names wild mango, African mango, or bush mango. They bear edible mango-like fruits, and are especially valued for their fat- and protein-rich nuts.

The fruit is a large drupe, with fibrous flesh. The subtly aromatic nuts are typically dried in the sun for preservation, and are sold whole or in powder form. They may be ground to a paste known variously as dika bread or Gabon chocolate. Their high content of mucilage enables them to be used as thickening agents for dishes such as ogbono soup. The nuts may also be pressed for vegetable oil.

The trees yield a hard wood, useful in construction.

The genus is named after Edward George Irving, a Royal Navy surgeon.

Table 2.7 Basic Information

Scientific Classification	
Kingdom	Plantae
(unranked)	Angiospermae
(unranked)	Eudicots
(unranked)	Rosids
Order	Malpighiales
Family	Irvingiaceae
Genus	Irvingia
Species	*Irvingia gabonensis*
Binomial Nomenclature	*Irvingia gabonensis*

Source Atangana, Tchoundjeu, Fondoun, Asaah, Ndoumbe& Leakey (2001)

2.3.2 Constituents

Several studies have assessed the chemical properties of the kernels or seeds and pulp in African mango.

An amino acid profile of fresh African mango seeds indicated the presence of 18 amino acids. Although phenotypic variations exist, physiochemical analysis documented that the seeds contain 3% moisture, 8% crude protein, 66% crude fat, 2% mineral ash, 10% crude fiber, and 11% carbohydrates. The oil content of the seed provided evidence for its use in industry, and the fiber content may provide bulk, improving bowel function Analysis of the pulp documented 80% moisture, 1% crude protein, 1% crude fat, 1% mineral ash, 0.5% crude fiber, and 11% carbohydrate. The high moisture content of the edible pulp provides evidence for its use in the production of juice, while the low ash content indicates a low mineral content. The seeds are a good source of nutrients, containing vitamins and minerals such as calcium, magnesium, potassium, sodium, phosphorus, and iron. The pulp is also an excellent source of calcium (262 mg per 100 g) and vitamin C (66.7 mg per 100 mL).

Aroma extract dilution analysis revealed 32 odor active volatile compounds that contribute to the overall nutty aroma of roasted seeds or kernels. Myristic, lauric, and palmitic acids compose nearly 95% of the total fatt y acids in African mango seeds. Margarine-based African mango oil may provide an alternative to t rans-fatty acids obtained during hydrogenation used in oil technological applications. Studies also evaluate the most efficient methods for dika nut cracking and whole kernel recovery.

Dika fat may serve a role in pharmaceutical drug-release systems. Dika fat out-performed magnesium stearate, stearic acid, and hydrogenated vegetable oil when tested in tablet equipment and imparted no adverse effect on the creation and integrity of hydrochlorothiazide tablets. Microencapsulation of aspirin with dika fat offered better protection against hydrolysis when compared with bee and carnauba wax. At 5% and 10% weight/weight wax concentrations, dika wax and paraffin wax were comparable in ability to delay drug release from microcapsules. Dika fat has also been evaluated as a film coating for drug release in polymeric systems. Suppositories containing dika fat blends satisfied pharmaceutical requirements of drug release and stability.

Studies document that mucilage extracted from African mango seeds performed better than acacia and tragacanth in emulsion and suspension formulations. Dika nut mucilage may improve tablet strength and drug-release properties in tablet formulations.

2.3.3 Ethnobotanical and Pharmacological Actions

There are a number of studies which put several pharmacological effects of into evident. The following are some of the prominent effects of *Irvingia gabonensis* seed extract

2.3.3.1 Anti obesity and lipid profile modurating effect:Ngondi J, Etoundi B, Nyangono C, Mbofung C, Oben J. IGOB131, a novel seed extract of the West African plant *Irvingia gabonensis*, significantly reduces body weight and improves metabolic parameters in overweight humans in a randomized double-blind placebo controlled investigation. Lipids In Health & Disease [serial online]. January 2009;8:1-7. Available from: Academic Search Premier, Ipswich, MA. Accessed September 25, 2012.

2.3.3.2 Modify cholesterol metabolism and increase HDL:Nangue T, Womeni H, Mbiapo F, Fanni J, Michel L. *Irvingia gabonensis* fat: nutritional properties and effect of increasing amounts on the growth and lipid metabolism of young rats wistar sp. Lipids In Health & Disease [serial online]. January 2011;10(1):43-53. Available from: Academic Search Premier, Ipswich, MA. Accessed September 25, 2012.

2.3.3.3 Reduce weight and improve metabolic parameter:Ross S. African mango (IGOB131): a proprietary seed extract of *Irvingia gabonensis* is found to be effective in reducing body weight and improving metabolic parameters in overweight humans. Holistic Nursing Practice [serial online]. July 2011;25(4):215-217. Available from: CINAHL Plus with Full Text, Ipswich, MA. Accessed September 25, 2012.

2.3.3.4 Weight loss:Oben J, Ngondi J, Momo C, Agbor G, Sobgui C. The use of a Cissusquadrangularis/*Irvingia gabonensis* combination in the management of weight loss: a double-blind placebo-controlled study. Lipids In Health & Disease [serial online]. January 2008;7:1-7. Available from: Academic Search Premier, Ipswich, MA. Accessed September 25, 2012.

2.3.3.5 Antimicrobial activity: Kuete V, Wabo G, Lall N, et al. Antimicrobial activity of the methanolic extract, fractions and compounds from the stem bark of *Irvingia gabonensis* (Ixonanthaceae). Journal of Ethnopharmacology [serial

online]. October 8, 2007;114(1), 54-60. Available from: CINAHL Plus with Full Text, Ipswich, MA. Accessed September 25, 2012.

2.3.3.6 Vasodepesrror effect: Nosiri C, Hussaini I, Abdu-Aguye I, Abdurahaman E. Pharmacological Effect of *Irvingia gabonensis* Leaf Extracts on Cat Blood Pressure. Internet Journal of Pharmacology [serial online]. September 2010;9(1):1. Available from: Academic Search Premier, Ipswich, MA. Accessed September 25, 2012.

2.3.3.7 Hypoglycemic effect: Omoruyi F, Adamson I. Effect of supplements of dikanut (*Irvingia gabonensis*) and cellulose on plasma lipids and composition of hepatic phospholipids in streptozotocin-induced diabetic rat. Nutrition Research [serial online]. April 1994;14:537-544. Available from: Biological & Agricultural Index Plus (H.W. Wilson), Ipswich, MA. Accessed September 25, 2012.

2.3.3.8 Hypoglycemic effect:Ozolua R, Eriyamremu G, Okene E, Ochei U. Hypoglycaemic effects of viscous preparation of *Irvingia gabonensis* (Dikanut) seeds in streptozotocin-induced diabetic wistar rats. Journal of Herbs, Spices & Medicinal Plants [serial online]. December 20, 2006;12(4):1-9. Available from: CINAHL Plus with Full Text, Ipswich, MA. Accessed September 25, 2012.

2.3.3.9 Anti diarrhea and anti ulcer: Raji Y, Ogunwande I, Adesola J, Bolarinwa A. Anti-Diarrhegenic and Anti-Ulcer Properties of *Irvingia gabonensis* in Rats. Pharmaceutical Biology [serial online]. October 2001;39(5):340. Available from: Academic Search Premier, Ipswich, MA. Accessed September 25, 2012.

2.3.4 Toxicity Assessment

Extract from the kernel (IGOB131) has been claimed for its health benefits. In the present investigations, potential adverse effects, if any, of IGOB131 were investigated in dose–response 90-day study and genotoxicity studies. In the subchronic study, Sprague Dawley rats (20/sex/group) were gavaged with I. gabonensis extract (IGOB131) at dose levels of 0, 100, 1000 and 2500mg/kg body weight (bw)/day for 90-days. No treatment-related changes in clinical signs, functional observations, mortality, ophthalmologic observations, body weights, body weight gain or feed consumption were noted. Similarly, hematological, clinical chemistry, urine analysis parameters, and organ weights did not reveal any toxicologically significant treatment-related changes. No treatment-related macroscopic and microscopic abnormalities were noted at the end of treatment period.

The mutagenicity as evaluated by Ames assay, in vitro and in vivo chromosomal aberration test and in vivo micronucleus assay did not reveal any genotoxicity of IGOB131. The results of subchronictoxicity study suggest the no-observed-adverse-effect level (NOAEL) for I. gabonensis extract (IGOB131) as ±2500mg/kg bw/day, the highest dose tested (Kothari S, Shivarudraiah P, Venkataramaiah S, Gavara S, Soni M. Subchronic toxicity and mutagenicity/genotoxicity studies of *Irvingia gabonensis* extract (IGOB131). Food & Chemical Toxicology [serial online]. May 2012;50(5):1468-1479. Available from: Academic Search Premier, Ipswich, MA. Accessed September 25, 2012)

CHAPTER 3

RESEARCH METHODOLOGY

3.1 Research Type

This research is an experimental study, designed to be a randomized, opened-label, controlled, crossover clinical trial.

3.2 Research Design

3.2.1 Subject selection: 14 participants were selected according to the designed criteria to join the experiment. They were randomized into 2 groups; the treatment group and control group.

3.2.2 Standard Intervention: Each participant from both groups ingested 75 grams of sucrose solution with a prepared beverage. The beverage given to the treatment group was *Irvingia gabonensis* extract solution while the control group was given water.

3.2.3 Result Measurements: Venous blood samples were collected from all participants for measurement of their blood glucose and insulin levels right before the ingestion and every 30 minutes afterward for a total of 6 times. (0, 30, 60, 90, 120, 150)

3.2.4 Adverse Event Monitoring: After the experiment, all participants kept a diary of severity of abdominal and other symptoms rated on a linear scale to monitor the effect of the beverages they received.

3.2.5 Crossover Intervention: After a washout period of 1 week, all participants repeated the test with the opposite treatment. This included result measurements and monitoring of adverse events.

3.3 Research Participants

3.3.1 Inclusion Criteria

3.3.1.1 Male or female subjects aged between 30 – 60 years old

3.3.1.2 No current active diseases of gastrointestinal tract, liver, kidney, allergy, and diabetes.

3.3.1.3 Participants were subjected to pass blood test of Blood Urea Nitrogen (BUN), serum creatinine, AST, ALT, ALP, fasting blood glucose, and complete blood count, physical examination and medical history record screening.

3.3.1.4 All blood test results, except fasting blood glucose, should display value within the normal reference range. The fasting blood glucose has to be less than the diagnostic diabetic level (126 mg/dL).

3.3.1.5 Subjects voluntarily participated in the study and signed their names in consent forms

3.3.2 Exclusion Criteria

3.3.2.1 History of being allergic or intolerant to *Irvingia gabonensis* products or derivatives

3.3.2.2 History of diseases of gastrointestinal tract, liver, kidney, allergy, and other diseases which may influence the bioavailability of *Irvingia gabonensis*'s active compounds

3.3.2.3 History of regular alcohol consumption or drug abuse

3.3.2.4 History of regular smoking

3.3.2.5 Subjects were under other medications a month prior to the study, particularly medications which alter the liver enzymes metabolism

3.3.2.6 Subjects have participated in other clinical trial a month prior to the study

3.3.3 Discontinuation Criteria

3.3.3.1 Subjects showed signs or symptoms of adverse reactions in which physician sees fit to discontinue from the study

3.3.3.2 Subjects did not follow the regulations of the study

3.3.3.3 Subjects would like to be discontinued from the study

3.3.4 Sample Size

Adequate sample size is defined by the following formula;

$$N = \frac{2(Z_{\frac{\alpha}{2}} + Z_{\beta})^2 \delta^2}{(x_1 - x_2)^2}$$

Providing that: X_1 = mean of group 1

X_2 = mean of group 2

δ^2 = pooled variance

$$\delta^2 = \frac{(n_1-1)S_1^2+(n_2-1)S_2^2}{n_1+n_2-2}$$

Given that: $\alpha = 0.05$; $Z_{\frac{\alpha}{2}} = 1.96$

$\beta = 0.10$; $Z_{\beta} = 1.28$

The calculation refers to the study of Joanna Hlebowicz, M.D., Gassan Darwiche, M.D., Ph.D., Ola Bjorgell, M.D., Ph.D., and Lars-OlofAlmer, M.D., Ph.D., which is a randomized crossover controlled trial on muesli with 4 g oat beta-glucan effect on postprandial plasma glucose by the use of Oral Glucose Tolerance Test (OGTT).

$n_1 = 12$ $n_2 = 12$

$x_1 = 39.4$ $x_2 = 54.8$

$S_1 = 7.8$ $S_2 = 14.9$

Evaluate the pooled variance $= \frac{(12-1)7.8^2+(12-1)14.9^2}{12+12-2} = 141.425$

$$N = \frac{2(1.96+1.28)^2 141.425}{(39.4-54.8)^2} = 12.52$$

According to the calculation, the adequate sample size for this research is at least 13. Therefore, this study employed 14 subjects.

3.4 Research Tools

The materials that were used in this study include the following:

3.4.1 Chemicals

3.4.1.1 *Irvingia gabonensis* capsule was provided by life extension.

3.4.1.2 75 grams of sucrose solution in 150 milliliters of water

3.4.2 Equipment

3.4.2.1 5 ml NaF plastic tube for blood plasma sample collection (For glucose measurement)

3.4.2.2 5 ml plastic tube for blood serum sample collection (For insulin measurement)

3.5 Research Procedures

3.5.1 Participants Preparation

3.5.1.1 Volunteers were screened for non-diabetic condition according to the inclusion and exclusion criteria.

3.5.1.2 Participants provided their personal profile.

3.5.1.3 Participants were explained about the detail and procedures of the study.

3.5.1.4 Participants willingly signed the informed consent form for clinical trial.

3.5.1.5 Participants were prohibited from consumptions of beverages containing alcohol and caffeine, smoking, and any food or beverage that may contain *Irvingia gabonensis* compounds a week prior to the test day.

3.5.1.6 Participants were required to fast after midnight prior to the test day.

3.5.2 Experiment Procedures

3.5.2.1 After at least 8 hours of fasting, participants were randomly divided into two groups by quota sampling.

3.5.2.2 Each participant from both groups ingested 75 grams of sucrose solution with a prepared beverage. The beverage given to the treatment group was *Irvingia gabonensis* while the control group was given warm water.

3.5.2.3 Blood samples were collected from all participants for measurement of their blood glucose and insulin levels right before the ingestion and 30 minutes, 60 minutes, 90 minutes, 120 minutes, and 150 minutes after the ingestion. NaF plastic tubes were used to collect blood sample for glucose levels measurement. Clotted blood, which was later separated into serum, was collected for insulin level measurement. The blood sample collection technique was venopuncture.

3.5.2.4 After the experiment, all participants kept a diary of severity of abdominal and other symptoms rated on a linear scale (0 = none through 4 = severe) to monitor the effect of the beverages they received.

3.5.2.5 After a washout period of 1 week, all participants repeated the test with the opposite treatment. This included result measurements and monitoring of adverse events.

3.6 Results Evaluation and Analysis

Blood glucose and insulin levels at different time points were compared between the treatment group and the control group. The area under the curve (AUC) was calculated for glucose and insulin for each subject. From the model of Oral Glucose Tolerance Test (OGTT), the whole body physiological insulin sensitivity was obtained (Matsuda & DeFronzo, 1999). This composite insulin sensitivity index (ISI-comp) is also referred to as the Matsuda Index.

Descriptive statistics were run on all measures, and the results are given as means ± SEM. All statistical calculations were performed using SPSS for Windows software (version 20.0.0, 2011). Statistics were verified for having normal distribution using One-Sample Kolmogorov-Smirnov test. Differences in blood glucose and insulin levels were evaluated with independent-samples t test.

After an 8-hour period after the ingestion of the *Irvingia gabonensis* solution or warm water, subjects ketp a record of their symptoms that might happen during the

period. The symptoms were rated on a linear scale of 0 (none) to 4 (severe). The included symptoms are as followed:

1. Headache
2. Fullness
3. Itching
4. Incomplete evacuation
5. Nausea
6. Excessive rectal gas
7. Fatigue
8. Bloating
9. Abdominal pain

The symptoms were compared between ingestion of *Irvingia gabonensis* solution and warm water. The comparisons were calculated for statistical significance with Pearson Chi-Square test. This study, employing 14 pre-diabetic subjects, set significance at $P < 0.05$.

CHAPTER 4

RESULTS

4.1 Baseline Demographic Data

There were 14 subjects participated in the study with ages ranging from 30 to 60 years old (Mean ± SD: 45.51 ± 7.45), as shown in Table 4.1. The gender was equally distributed, with 7 males and 7 females. The average body mass index of the subjects reflects a slightly overweight group of individuals (Mean ± SD: 25.59 ± 2.57). Blood pressure, heart rate, body temperature, complete blood counts, and other blood chemistry profiles were all within normal ranges.

Table 4.1 Characteristics of Study Subjects at Baseline

Parameter	Value
Total Number, M/F (n/n)	14 (7/7)
Age (years)	45.51 ± 7.45
BMI (kg/m^2)	25.59 ± 2.57
Systolic BP (mmHg)	118.35 ± 16.48
Diastolic BP (mmHg)	79.49 ± 9.25
Heart rate (BPM)	65.32 ± 8.32
Temperature (˚C)	36.18 ± 0.42
CBC	
Hematocrit (%)	41.32 ± 3.96
Hemoglobin (g/dL)	13.32 ± 1.15
RBC ($10^6/mm^3$)	4.32 ± 0.58
WBC ($10^3/mm^3$)	5.97 ± 1.31
Platelet ($10^3/mm^3$)	252.50 ± 66.37

Table 4.1 (continued)

Parameter	Value
Blood chemistry	
Fasting glucose (mg/dL)	102.77 ± 4.72
BUN (mg/dL)	11.77 ± 3.52
Creatinine (mg/dL)	0.72 ± 0.13
AST (U/L)	19.57 ± 3.60
ALT (U/L)	22.67 ± 7.37
ALP (U/L)	69.23 ± 18.84
Educational level	
Elementary school	2 (14.28%)
High school	5 (35.70%)
Bachelor's degree	5 (35.70%)
Master degree or higher	2(14.28%)
Marital status	
Single	3(21.42%)
Married	8(57.12%)
Divorced	2(14.28%)
Widowed	1 (7.14%)
Allergic history	
Yes	2 (14.28%)
No	13 (85.72%)
Having underlying diseases	
Yes	2 (14.28%)
No	12 (85.72%)
Family DM history	
Yes	6 (42.84%)
No	8 (57.16%)

Table 4.1 (continued)

Parameter	Value
Having gestational DM history	
Yes	0 (0%)
No	14 (100%)
Having impaired fasting glucose history	
Yes	10 (71.43%)
No	4 (28.57%)
Smoking	
None	14 (100%)
Rarely	0 (0%)
Sometimes	0 (0%)
Frequently	0 (0%)
Alcohol intake	
None	10 (71.40%)
Rarely	3(21.42%)
Sometimes	1 (7.14%)
Frequently	0 (0%)
Soft drink intake	
None	6 (42.84%)
Rarely	3 (21.42%)
Sometimes	5 (35.70%)
Frequently	1 (7.14%)
Physical activity (Exercise)	
None	3 (21.42%)
Rarely	5 (35.70%)
Sometimes	5 (35.70%)
Frequently	1 (7.14%)

Note. Values are shown as mean ± SD.

Table 4.1 displays an array of characteristic of the participants recorded at baseline. Most subjects do not have underlying diseases (85.72%), but 42.84 of them have familial history of diabetes. All of the subjects do not smoke, and most of them do not drink alcohol. Most subjects reported nearly do enoghexcdercise.

4.2 Postprandial Glucose and Insulin Response

After oral glucose tolerance test, the sample group which received *Irvingia gabonensis* water prior to the tolerance test tends to have a lower level of plasma glucose and serum insulin concentrations compared to the controlled group, with significant difference. The mean difference of the incremental glucose level at each time point also tends to be lower for the *Irvingia gabonensis* group, with significant difference at 30, 60, 90, 120, 150 min time point, shown in Table 4.3 and Figure 4.2. Th

4.2.1 Levels and Mean Difference, of Glucose and Insulin of all Subjects

Table 4.2 and Figure 4.1 illustrate the effect of *Irvingia gabonensis* versus water on the concentration of plasma glucose in non-diabetic subjects. It can be seen that plasma glucose levels for the *Irvingia gabonensis* sample group tends to be lower than the water group, with less steep rise and fall (fluctuation). And, the difference is significant

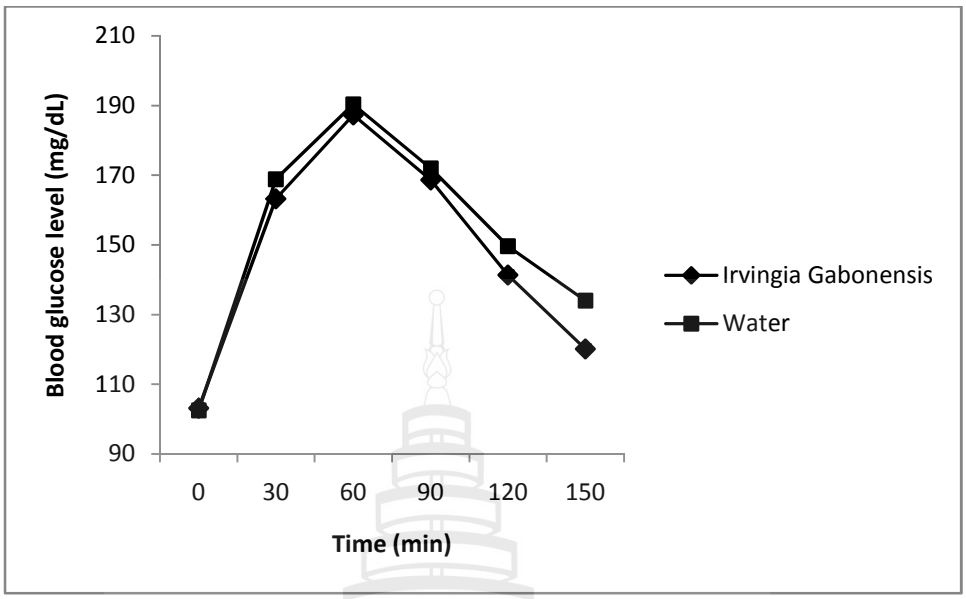
Table 4.3 and Figure 4.2 show the mean difference value for the incremental concentration of plasma glucose compared to baseline (T0). This data represents the change in blood glucose level over time. It can be seen that the change in blood glucose for the water group is greater, with significant difference during the 30 minutes ($P<$ 0.01) 60 minute (0.008) 90 minutes (0.039) 120 minutes(0.019) 150 minutes (<0.001). During the first 30 minutes of OGTT, the glucose levels of the *Irvingia gabonensis* sample group raised 60.14 ± 1.24 mg/dL on average, as compared to a rise of 66.32 ± 0.73 mg/dL for the water sample group. During the 60 minutes of OGTT, the glucose levels of the *Irvingia gabonensis* sample group raised 84.20 ± 0.62 mg/dL on average, as compared to a rise of 87.79 ± 1.07mg/dLfor the water sample group. During the 90 minutes of OGTT, the glucose levels of the *Irvingia gabonensis* sample group raised 65.49 ± 1.46 mg/dL on average, as compared to a rise of 69.41 ± 1.05mg/dL for the water sample group. During the 120 minutes of OGTT, the glucose levels of the *Irvingia*

gabonensis sample group raised 38.26 ± 3.26 mg/dL on average, as compared to a rise of 47.14 ± 1.37mg/dL for the water sample group. During the 150 minutes of OGTT, the glucose levels of the *Irvingia gabonensis* sample group raised 17.01 ± 2.03 mg/dL on average, as compared to a rise of 31.53 ± 1.35mg/dL for the water sample group.

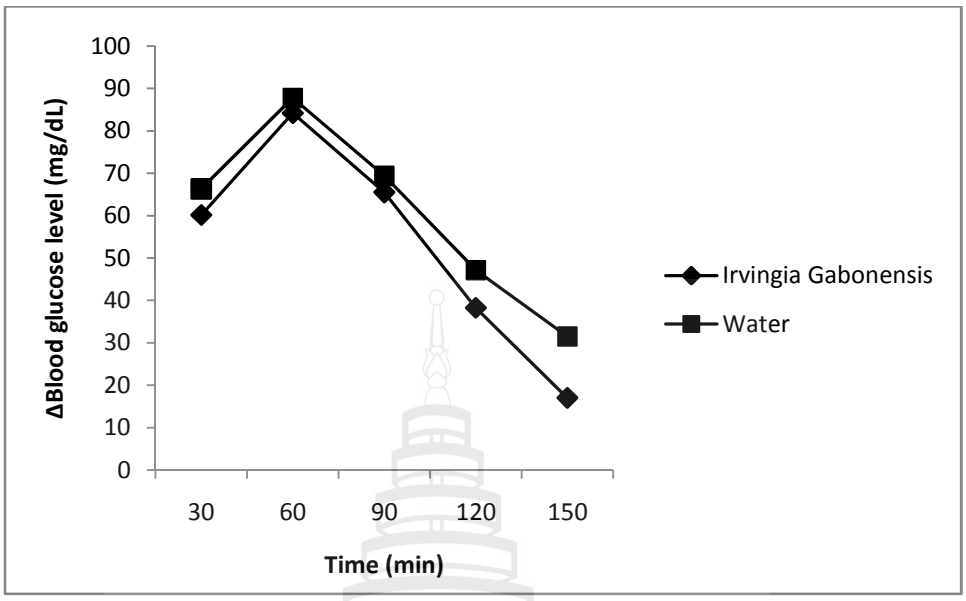
Table 4.2 Plasma Glucose Levels of the Subjects during Oral Glucose ToleranceTest after Ingesting either *Irvingia Ganonensis* Solution or Water

Time point (min)	**Plasma glucose level (mg/dL)**		***P*-value Between group**
	***Irvingia Gabonensis* solution**	**water**	
T0	103.09 ± 1.21	102.46 ± 1.32	0.731
T30	163.23 ± 1.79	168.79 ± 1.15	0.015
T60	187.28 ± 0.67	190.25 ± 1.02	0.022
T90	168.57 ± 1.05	171.88 ± 1.30	0.059
T120	141.35 ± 2.78	149.60 ± 0.68	0.012
T150	120.10 ± 1.00	133.99 ±1.30	<0.001

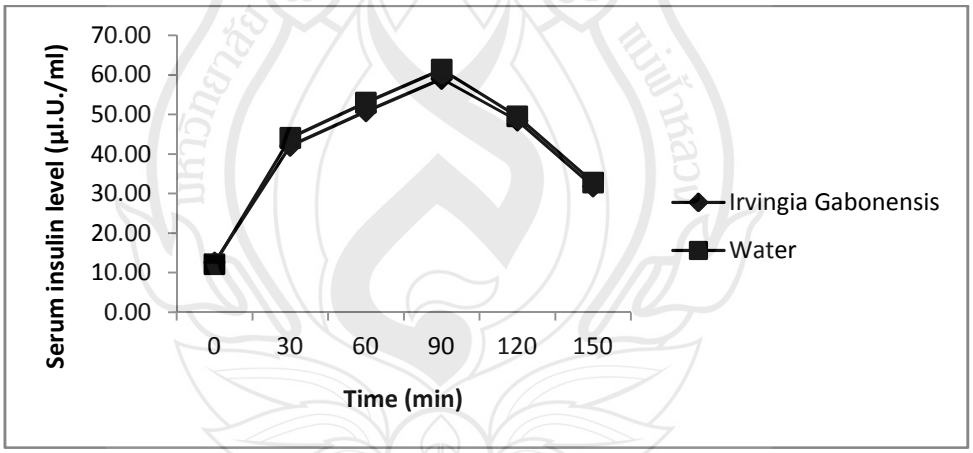
Note. Values are shown as mean ± SEM. Some significant difference is found between the 2 groups (P<0.05).



Time point (min)	Mean difference of plasma glucose level (mg/dL)		*P*-value
	Irvingia Gabonensis solution	Warm	Between group
T0-30	60.14 ± 1.24	66.32 ± 0.73	<0.01
T0-60	84.20 ± 0.62	87.79 ± 1.07	0.008
T0-90	65.49 ± 1.46	69.41 ± 1.05	0.039
T0-120	38.26 ± 3.26	47.14 ± 1.37	0.019
T0-150	17.01 ± 2.03	31.53 ± 1.35	<0.001


100
90
80
70
60
50
40
30
20
10
0
ΔBlood glucose level (mg/dL)
30
60
90
120
150
Time (min)
Irvingia Gabonensis
Water

Time point (min)	Serum insulin level (µI.U./ml)		*P*-value
	Irvingia Gabonensis	Warm water	Between group
T0	12.53 ± 0.26	12.18 ± 0.17	0.248
T30	42.01 ± 0.88	44.07 ± 0.91	0.114
T60	50.71 ± 1.05	52.97 ± 0.78	0.097
T90	58.93 ± 1.02	61.31 ± 0.86	0.086
T120	48.42 ± 1.21	49.53 ± 1.01	0.486
T150	31.74 ± 0.47	32.78 ± 0.48	0.134



Time point (min)	Mean difference of serum insulin level (µI.U./ml)		*P*-value Between group
	Irvingia Gabonensis	Water	
T0-30	29.48 ± 0.99	31.89 ± 0.90	0.084
T0-60	38.19 ± 1.20	40.78 ± 0.82	0.086
T0-90	46.40 ± 1.16	49.12 ± 0.87	0.072
T0-120	35.89 ± 1.21	37.35 ± 1.02	0.367
T0-150	19.21 ± 0.44	20.60 ± 0.53	0.056

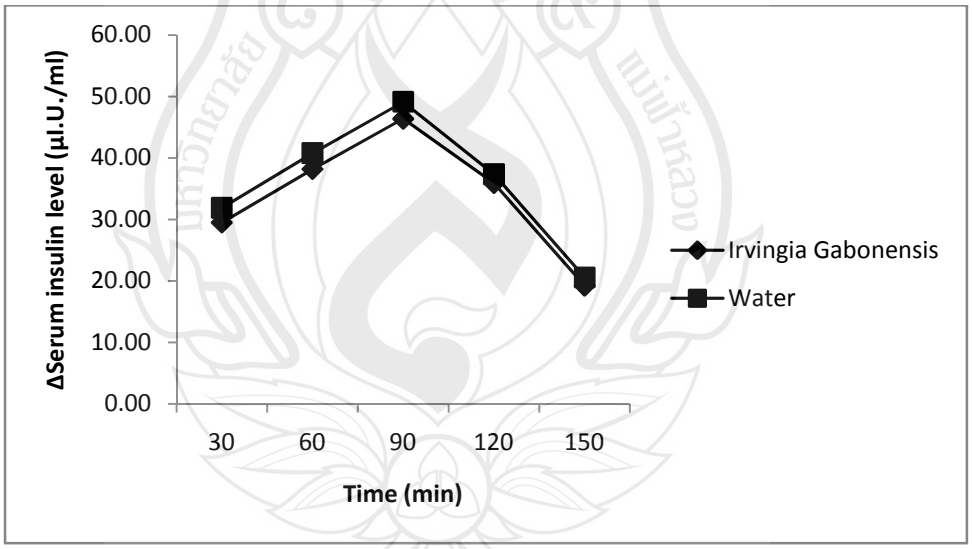


Table 4.6 Adverse Events 8 Hours Post Experiment, Reported by Subjects

Symptom		*Irvingia Gabonensis* group	Warm water group	*P*-value Between group
Headache	None	12 (85.71%)	14 (100.00 %)	0.481
	Mild	2 (14.29%)	0 (0.00%)	
Fullness	None	11 (78.57%)	11 (78.57%)	1.000
	Mild	3 (71.43%)	3 (21.43%)	
Itching	None	14 (100.00%)	14 (100.00%)	N/A
	Mild	0 (0.00%)	0 (0.00%)	
Incomplete evacuation	None	13 (92.86%)	14 (100.00 %)	1.000
	Moderate	1 (7.14%)	0 (0.00%)	
Nausea	None	12 (85.71%)	13 (92.86%)	1.000
	Mild	2 (14.29 %)	1 (7.14%)	
Excessive rectal gas	None	11 (78.57%)	12 (85.71%)	1.000
	Mild	3 (21.43 %)	2 (14.29%)	
Fatigue	None	12 (85.71%)	12 (85.71%)	1.000
	Mild	1 (7.14%)	1 (7.14%)	
	Moderate	1 (7.14%)	1 (7.14%)	
Bloating	None	12 (85.71%)	13 (92.86%)	1.000
	Mild	1 (7.14%)	1 (7.14%)	
	Moderate	1 (7.14%)	0 (0.00%)	
	Severe	0 (0.00%)	0(0.00%)	
Abdominal pain	None	13 (92.86%)	13 (92.86%)	1.000
	Mild	1 (7.14%)	1 (7.14%)	

CHAPTER 5

DISCUSSION, CONCLUSION AND SUGGESTIONS

5.1 Discussion

The primary endpoint in this study was the effect of *Irvingia gabonensis* solution on postprandial glucose and insulin levels in non-diabetic subjects. The author's hypothesis was that *Irvingia gabonensis* could lower postprandial glucose and insulin level, as well as improving the whole body physiological insulin sensitivity in non-diabetic subjects. Several prospective studies, *in vivo* and *in vitro* experiments have been done regarding *Irvingia gabonensis* properties and its pharmacological potentials. The most strongly supported mechanism of *Irvingia gabonensis* extract is its ability to cause carbohydrate maldigestion and malabsorption (Omoruyi F, Adamson I. Effect of supplements of dikanut (*Irvingia gabonensis*) and cellulose on plasma lipids and composition of hepatic phospholipids in streptozotocin-induced diabetic rat. Nutrition Research [serial online]. April 1994;14:537-544. Available from: Biological & Agricultural Index Plus (H.W. Wilson), Ipswich, MA. Accessed September 25, 2012.)

Based on Table 4.2 and Table 4.4, the author did observe significant difference in glucose during 30 minutes, 60 minutes,120 minutes and 150 minutes but without significant in insulin. Although the trends of insulin parameters seem to be lower for the *Irvingia gabonensis* group, the difference is subtle.

The mean differences of incremental glucose values compared to baseline are different, with statistical significance during the first 30 minutes , 60 minutes , 90 minutes , 120 minutes and 150 minutes of the test), shown in Table 4.3. During the time of the test of OGTT , the glucose level of *Irvingia gabonensis* group raise lower than water group with statistical significant. This statistic implies that consumption of *Irvingia gabonensis* may aid in postprandial glycemic control during the 180 minutes after meal.

Base on Table 4.5 despite the insignificant difference of insulin level between *Irvingia gaboenesis* group and the control group, the result of each individual subject shows that the *Irvingia gabonensis* sample group has a lower insulin l compared to the control group.

Base on The table 4.6 there is no significant adverse side effect of *Irvingia gabonensis* during the experiment.

5.2 Conclusion

In non-diabetic subjects, consumption of *Irvingia gabonensis* aid in postprandial glycemic control during the 30, 60, 120, 180 minutes after meal. However *Irvingia gaboenesis* does not influence the physiological insulin sensitivity and does not cause significant adverse events.

5.3 Suggestions

5.3.1 Clinical trial with long length of monitoring:

There have been a number of researches which were conducted using *Irvingia gabonensis* on rat but not a single data on human. It is interesting to track long-term parameters which involve risks of diabetes and diabetes management, including fasting plasma glucose, fasting insulin, glycated hemoglobin levels (HbA1C), triglycerides, and etc.

5.3.2 Comparison of *Irvingia Gabonensis* and Antidiabetic Medicine:

For the purpose of treatment and prophylaxis of diabetes, it is essential to evaluate the advantages and disadvantages of choosing between *Irvingia gabonensis* or extract and other antidiabetic drugs with similar mechanism of actions, including glybutamide, metformin, acarbose, voglibose, and etc. Potency and severity of adverse events should be compared for the optimal benefits of diabetes treatment and prevention.

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APPENDICES

APPENDIX A

INFORMED CONSENT FORM

หนังสือยินยอมเข้าร่วมโครงการวิจัย(Informed Consent Form)

วันที่…… เดือน……. พ.ศ. .....

ข้าพเจ้า นาย/นางสาว/นาง อายุ …… ปี

อยู่บ้านเลขที่ ……. หมู่ที่ ……..…….. ถนนตำบล .....

อำเภอ..... จังหวัด …….. รหัสไปรษณีย์ .....

โทรศัพท์ ……...ขอทำหนังสือแสดงความยินยอมเข้าร่วมโครงการวิจัยเพื่อเป็นหลักฐานแสดงว่า

1. ข้าพเจ้ายินยอมเข้าร่วมโครงการวิจัยของ (หัวหน้าโครงการ) นายเอนก โซนี่ เรื่อง “ผลของสมุนไพร *IrvingiaGabonensis*ต่อการควบคุมระดับน้ำตาลในเลือด และความไวต่ออินซูลินในผู้ที่มีระดับน้ำตาลในเลือดสูง” ด้วยความสมัครใจ โดยมิได้มีการบังคับ หลอกลวงแต่ประการใด และพร้อมจะให้ความร่วมมือในการวิจัย

2. ข้าพเจ้าได้รับการอธิบายและตอบข้อสงสัยจากผู้วิจัยเกี่ยวกับวัตถุประสงค์การวิจัย วิธีการวิจัย ความปลอดภัย อาการ หรืออันตรายที่อาจเกิดขึ้น รวมทั้งประโยชน์ที่จะได้รับจากการวิจัย โดยละเอียดแล้วตามเอกสารชี้แจงผู้เข้าร่วมการวิจัยแนบท้าย

3. ข้าพเจ้าได้รับการรับรองจากผู้วิจัยว่าจะเก็บข้อมูลส่วนตัวของข้าพเจ้าเป็นความลับ จะเปิดเผยได้เฉพาะในรูปแบบของการสรุปผลการวิจัยเท่านั้น

4. ข้าพเจ้าได้รับทราบจากผู้วิจัยแล้วว่า หากเกิดอันตรายใดๆ จากการวิจัย ผู้วิจัยจะรับผิดชอบค่ารักษาพยาบาลที่เป็นผลสืบเนื่องจากการวิจัยนี้

5. ข้าพเจ้าได้รับทราบว่า ข้าพเจ้ามีสิทธิที่จะถอนตัวออกจากการวิจัยครั้งนี้เมื่อใดก็ได้ โดยไม่มีผลกระทบใดๆ ต่อการรักษาพยาบาลตามสิทธิ์ที่ข้าพเจ้าควรได้รับ

ข้าพเจ้าได้อ่านและเข้าใจข้อความตามหนังสือนี้แล้ว จึงได้ลงลายมือชื่อไว้เป็นสำคัญ พร้อมกับหัวหน้าโครงการวิจัยและพยาน

ลงชื่อ ..... ผู้ยินยอม

(.....)

ลงชื่อ ..... หัวหน้าโครงการ

(.....)

ลงชื่อ ..... พยาน

(.....)

ลงชื่อ .....พยาน

(.....)

APPENDIX B

INFORMATION

เอกสารชี้แจงโครงการวิจัยแก่ผู้เข้าร่วมการวิจัย

ในเอกสารนี้อาจมีข้อความที่ท่านอ่านแล้วยังไม่เข้าใจ โปรดสอบถามหัวหน้าโครงการวิจัยให้ช่วยอธิบายจนกว่าจะเข้าใจดี ท่านอาจจะขอเอกสารนี้กลับไปอ่านที่บ้านเพื่อปรึกษาหารือกับญาติพี่น้อง เพื่อนสนิท แพทย์ประจำตัวของท่าน หรือแพทย์ท่านอื่น เพื่อช่วยในการตัดสินใจเข้าร่วมการวิจัย

ชื่อโครงการ: ผลของ *IrvingiaGabonensis*ต่อการควบคุมระดับน้ำตาลในเลือด และความไวต่ออินซูลินในผู้ที่มีระดับน้ำตาลในเลือดสูง

ชื่อผู้วิจัย: นายเอนก โซนี่

ท่านได้รับเชิญให้เข้าร่วมการศึกษาวิจัยเรื่อง “ผลของชาใบหม่อนต่อการควบคุมระดับน้ำตาลในผู้ที่มีระดับน้ำตาลในเลือดสูง” การศึกษาวิจัยนี้ทำโดย นายแพทย์ เอนก โซนี่ กรุงเทพมหานคร คาดไว้ว่าจะมีอาสาสมัครเข้าร่วมการศึกษาวิจัยในครั้งนี้จำนวน 14 ราย

วัตถุประสงค์ของโครงการวิจัย

การศึกษาวิจัยนี้ทำขึ้นเพื่อวัดผลของ “ชาใบหม่อน” ในการลดระดับน้ำตาลในเลือดและเพิ่มประสิทธิภาพการใช้อินซูลินของร่างกาย

การศึกษานี้ใช้ระยะเวลาในการศึกษา 3 สัปดาห์ โดยท่านต้องเข้าพบผู้วิจัยจำนวน 3 ครั้ง ครั้งละ 1 วัน เว้นระยะเวลาระหว่างการเข้าพบแต่ละครั้ง 1 สัปดาห์ และท่านจำเป็นต้องอยู่ที่ศูนย์การศึกษาเป็นเวลาประมาณ 4.5 ชั่วโมงสำหรับการเข้าพบแต่ละครั้ง ท่านจะได้รับเครื่องดื่มที่ใช้ในการศึกษาวิจัย คือ “*IrvingiaGabonensis*” หรือ “น้ำเปล่า” ในแต่ละครั้งที่เข้าร่วมการศึกษา และจะได้รับสารละลายน้ำตาลซูโครส (น้ำเชื่อม) ครึ่งชั่วโมงให้หลังจากการ ดื่มสารทดลอง

สถานที่วิจัย สถานที่ทำงานและหมายเลขโทรศัพท์ที่ติดต่อได้ทั้งในและนอกเวลาราชการ

ศูนย์การแพทย์ absolutehealthclinicกรุงเทพมหานครโทรศัพท์ 086-6712255

สิ่งที่ท่านต้องปฏิบัติเมื่อเข้าร่วมโครงการวิจัยนี้

หากท่านสมัครใจที่จะเข้าร่วมการศึกษาวิจัยนี้ จะมีขั้นตอนที่จะต้องปฏิบัติดังนี้คือ:

1. ท่านจะถูกร้องขอให้อ่าน ลงนามและลงวันที่ในหนังสือแสดงความยินยอม หลังจากที่ท่านได้รับการอธิบาย และการตอบคำถามจากผู้วิจัยเป็นที่เรียบร้อยแล้ว

2. การเข้าพบครั้งที่ 1 (การคัดเลือก)

หากท่านยินยอมที่จะเข้าร่วมการศึกษาวิจัย และได้อ่านและลงนามในเอกสารชี้แจงผู้เข้าร่วมโครงการวิจัยและหนังสือให้ความยินยอมเป็นที่เรียบร้อยแล้ว ผู้วิจัยจะทำการตรวจเพื่อดูว่าท่านเหมาะสมที่จะเข้าร่วมการวิจัยได้หรือไม่ การตรวจวัดนี้รวมถึงการทบทวนประวัติทางการแพทย์ของท่าน การตรวจร่างกาย จะมีการเจาะเลือดประมาณ 15 มิลลิลิตร (1 ช้อนโต๊ะ) ทางหลอดเลือดดำที่แขนของท่าน เพื่อไปหาค่าตรวจทางห้องปฏิบัติการอีกด้วย

<u>ท่านจะไม่ได้รับอนุญาตให้ดื่มเครื่องดื่มที่มีคาเฟอีนเป็นองค์ประกอบ เช่น กาแฟ ชา เครื่องดื่มบำรุงกำลัง หรือแอลกอฮอล์ สูบบุหรี่ และรับประทานหรือดื่มอาหารใดๆที่มีส่วนประกอบของใบหม่อนเป็นระยะเวลา 1 สัปดาห์ก่อนวันทดสอบ คือการตรวจครั้งที่ 2</u>

<u>ท่านจะต้องทำการงดน้ำและอาหารหลังจากเวลาเที่ยงคืนในคืนก่อนวันทดสอบ คือการตรวจครั้งที่ 2</u>

3. การเข้าพบครั้งที่ 2

ในการตรวจครั้งนี้ ท่านจะได้รับการตรวจวัดน้ำหนัก อุณหภูมิร่างกาย ความดันเลือด และอัตราการเต้นของหัวใจ และหากท่านมีคุณสมบัติครบถ้วนตามเกณฑ์ ท่านจะถูกสุ่มเลือกว่าจะได้รับการทดสอบด้วย *IrvingiaGabonenisis* หรือน้ำอุ่น จากนั้นผู้วิจัยจะขอให้ท่านดื่มเครื่องดื่มตามที่ท่านถูกสุ่มเลือกให้ได้รับ (ชาใบหม่อนหรือน้ำอุ่น) และหลังจากนั้นเป็นเวลา 30 นาที ท่านจะถูกขอให้ดื่มสารละลายน้ำตาลซูโครส (น้ำเชื่อม)

จะมีการเจาะเลือดทางหลอดเลือดดำที่แขนของท่านผ่านทางชุดอุปกรณ์ที่ใช้ป้องกันการแข็งตัวของเลือดที่เรียกว่า “เฮ็พพาริน ล็อค” ซึ่งมีลักษณะเป็นอุปกรณ์ขนาดเล็กที่ใส่คาหลอดเลือดดำไว้สำหรับเก็บเลือดทางหลอดเลือดดำเป็นระยะๆจะมีการเก็บเลือดของท่านจำนวน 6 ครั้ง คือ ที่เวลาก่อนเริ่มดื่มสารละลายซูโครส (น้ำเชื่อม) และ *IrvingiaGabonensis* หรือน้ำอุ่น และในนาทีที่ 30, 60, 90, 120 และ 150 หลังการดื่ม ปริมาณเลือดที่เก็บในแต่ละครั้งคือ 2 ซี.ซี.

หลังการเก็บเลือดในนาทีที่ 150 ท่านจะถูกขอให้อยู่ต่อในศูนย์วิจัยเป็นเวลาอย่างน้อยอีก 30 นาที เพื่อสังเกตอาการไม่พึงประสงค์ใดๆที่อาจจะเกิดขึ้น

ท่านจะถูกขอให้จดบันทึกอาการข้างเคียงที่อาจจะเกิดขึ้นในระบบทางเดินอาหารหรือระบบอื่นๆของร่างกายภายในช่วงเวลา 8 ชั่วโมงหลังการทดสอบ

<u>ท่านจะถูกขอให้กลับมาที่ศูนย์วิจัยในอีก 7 วันข้างหน้า โดยท่านจำเป็นต้องงดน้ำและอาหารหลังเวลาเที่ยงคืนในคืนก่อนวันทดสอบ คือการเข้าพบครั้งที่ 3</u>

ท่านจะไม่ได้รับอนุญาตให้ดื่มเครื่องดื่มที่มีคาเฟอีนเป็นองค์ประกอบ เช่น กาแฟ ชา เครื่องดื่มบำรุงกำลัง หรือแอลกอฮอล์ สูบบุหรี่ และรับประทานหรือดื่มอาหารใดๆที่มีส่วนประกอบของ *IrvingiaGabonensis* เป็นระยะเวลา 1 สัปดาห์ก่อนวันทดสอบ คือการเข้าพบครั้งที 3

4. การเข้าพบครั้งที่ 3 (1 สัปดาห์หลังจากได้รับการรักษาครั้งแรก)

ในการตรวจครั้งนี้ ท่านจะได้รับการตรวจวัดน้ำหนัก อุณหภูมิร่างกาย ความดันเลือด และอัตราการเต้นของหัวใจ และการเจาะเลือดผ่านอุปกรณ์ “เฮ็พพาริน ล็อค” เช่นเดียวกับการทดสอบครั้งที่แล้ว

จะมีการสลับชนิดของเครื่องดื่มที่ท่านได้รับ คือหากครั้งที่แล้วท่านได้รับ *IrvingiaGaboenesis* การทดสอบในครั้งนี้ท่านจะได้รับน้ำอุ่นหรือในทางกลับกัน หลังจากนั้น 30 นาที ผู้วิจัยจะขอให้ท่านดื่มสารละลายน้ำตาลซูโครส (น้ำเชื่อม) เช่นเดิม แต่

หลังการเก็บเลือดในนาทีที่ 150 ท่านจะถูกขอให้อยู่ต่อในศูนย์วิจัยเป็นเวลาอย่างน้อยอีก 30 นาที เพื่อสังเกตอาการไม่พึงประสงค์ใดๆที่อาจจะเกิดขึ้น

ท่านจะถูกขอให้จดบันทึกอาการข้างเคียงที่อาจจะเกิดขึ้นในระบบทางเดินอาหารหรือระบบอื่นๆของร่างกายภายในช่วงเวลา 8 ชั่วโมงหลังการทดสอบ และขอให้ท่านส่งแบบฟอร์มการจดบันทึกให้ผู้วิจัยทางไปรษณีย์ โดยใช้ซองจดหมายที่ทางผู้วิจัยเตรียมไว้ให้

การตรวจเมื่อมีการถอนตัวออกจากการศึกษาวิจัยก่อนกำหนด

หากแพทย์มีความเห็นถอนตัวท่านออกจากการศึกษาวิจัยก่อนกำหนดการสิ้นสุดการศึกษาวิจัย ท่านจะได้รับการร้องขอให้ทำการตรวจประเมินที่กำหนดไว้ในการตรวจครั้งที่ 2 เมื่อเวลาที่ถอนตัวออกจากการศึกษาวิจัย

ข้อจำกัดในการดำเนินชีวิตระหว่างการเข้าร่วมโครงการ

ท่านจะไม่ได้รับอนุญาตให้ดื่มเครื่องดื่มที่มีคาเฟอีนเป็นองค์ประกอบ เช่น กาแฟ ชา เครื่องดื่มบำรุงกำลัง หรือแอลกอฮอล์ สูบบุหรี่ และรับประทานหรือดื่มอาหารใดๆที่มีส่วนประกอบของใบหม่อนเป็นระยะเวลา 1 สัปดาห์ก่อนวันทดสอบทั้ง 2 ครั้งและท่านจะได้รับการร้องขอให้กลับมาที่หน่วยการศึกษาสัปดาห์ละครั้ง ติดต่อกันเป็นระยะเวลา 2 สัปดาห์

ประโยชน์ที่อาจเกิดขึ้นเมื่อเข้าร่วมการศึกษาวิจัย

ไม่มีการรับประกันว่าท่านจะได้รับประโยชน์โดยตรงจากการศึกษาวิจัยนี้ ความรู้เพิ่มเติมที่ได้จากการศึกษาวิจัยในครั้งนี้อาจเป็นการให้ข้อมูลเกี่ยวกับการใช้ “*IrvingiaGabonensis*” ในบุคคลทั่วไป

ความเสี่ยงและความไม่สบายที่อาจจะเกิดขึ้นเมื่อเข้าร่วมการศึกษาวิจัย

ขั้นตอนในการศึกษาวิจัยอาจมีผลเกี่ยวข้องในการทำให้เกิดความเสี่ยง และความไม่สบายบางอย่างได้ "*IrvingiaGabonensis*" ที่ใช้ในการศึกษาวิจัยสามารถทำให้เกิดอาการข้างเคียงได้แม้ได้ใช้ตามที่แนะนำไว้ เพื่อประโยชน์สูงสุดของตัวท่าน แพทย์อาจสั่งจ่ายยาอื่นเพิ่มเติมจากยาที่ใช้ในการศึกษาวิจัย เพื่อบรรเทาอาการข้างเคียงของท่าน มีความเป็นไปได้ว่าอาจเกิดอาการแทรกซ้อนและอาการข้างเคียงที่ไม่เคยปรากฏมาก่อนในการศึกษาวิจัยครั้งนี้

"*IrvingiaGabonensis*"

อาการข้างเคียงที่อาจเกิดขึ้นได้จากการดื่มสารละลาย *IrvingiaGabonensis* ได้แก่ อาการของระบบทางเดินอาหารและลำไส้ อาจทำให้ท้องเสียได้ อาจทำให้อุจจาระเหลวเมื่อได้รับคู่กับน้ำตาลในปริมาณมาก อาจเกิดเสียงในลำไส้หรือท้องอืดเหมือนกับการรับประทานพืชที่มีฝัก เช่นถั่วหรือผักสด อาจทำให้รู้สึกอิ่ม หรือแน่นท้อง ซึ่งหากเกิดอาการเหล่านี้ขึ้น อาการเหล่านี้จะลดลงและหายไปเองภายในช่วงสั้นๆ สารแทนนินในชาอาจทำให้เกิดอาการท้องผูกได้

"การเจาะเลือด"

มีความเสี่ยงเล็กน้อยในการทำให้เกิดอาการปวด หรือช้ำ และติดเชื้อในบริเวณที่มีการเจาะเลือด

ข้อมูลที่ได้จากการศึกษาวิจัย

ในทุกแง่มุมของการศึกษาวิจัย รวมถึงผลที่ได้จากการศึกษาวิจัย จะถูกเก็บรักษาไว้เป็นความลับสุดยอด มีเพียงเฉพาะผู้วิจัยเท่านั้นที่จะสามารถเข้าถึงข้อมูลของผู้เข้าร่วมการศึกษาวิจัย รายงานการศึกษาวิจัยอาจตีพิมพ์ได้ แต่ข้อมูลของผู้เข้าร่วมการศึกษาวิจัยจะไม่สามารถถูกพิสูจน์ได้

ค่าใช้จ่ายในการเข้าร่วมการศึกษาวิจัย

ผู้วิจัยจะเป็นผู้ออกค่า "*IrvingiaGabonensis*" ค่าตรวจทางห้องปฏิบัติการและค่าตรวจอื่นที่เกี่ยวข้องกับการศึกษาวิจัย สำหรับค่าใช้จ่ายอื่นๆที่เกิดขึ้นจากขั้นตอนการรักษาตามปกติ ท่านจะต้องเป็นผู้รับผิดชอบ

การจ่ายค่าตอบแทน

ท่านจะได้รับค่าเดินทางเพื่อการวิจัยต่อการเข้าพบแพทย์ตามเวลาที่กำหนดไว้ครั้งละ 200 บาท

ความช่วยเหลือที่ท่านจะได้รับหากได้รับอันตรายจากยา

หากท่านได้รับการเจ็บป่วยที่เกิดเนื่องจากชาใบหม่อนที่ใช้ในงานวิจัย หรือในกรณีที่เกิดภาวะแทรกซ้อน ท่านจะได้รับการดูแลรักษาที่เหมาะสมตามสมควรจะได้รับที่เกี่ยวข้องกับการบาดเจ็บนั้น โดยทางผู้วิจัยวิจัยจะเป็นผู้ออกค่าใช้จ่ายต่างๆ อันเกิดจากการเจ็บป่วยที่เป็นผลมาจากยาที่ใช้ในการศึกษาวิจัย แต่ท่านจะไม่ได้รับค่าชดเชยใดๆ หากท่านเชื่อว่าท่านได้รับอันตรายจากชาใบ

หม่อนที่ใช้ในงานวิจัย ท่านสามารถสอบถามข้อมูลเพิ่มเติมกับผู้วิจัยได้ทุกเมื่อ โดยกรุณาติดต่อ นายปริวรรต ศุกรีเขตร เบอร์โทรศัพท์ 086-6712255 ได้ตลอด 24 ชั่วโมง

การตัดสินใจและสิทธิของท่าน

การเข้าร่วมการศึกษาในครั้งนี้เกิดขึ้นจากความสมัครใจโดยทั้งหมด ท่านจะไม่ถูกบังคับให้เข้าร่วมการศึกษาวิจัยในครั้งนี้ และเมื่อท่านเข้าร่วมการศึกษาแล้วท่านมีสิทธิที่จะถอนตัวออกจากการศึกษาเมื่อใดก็ได้ การตัดสินใจใดๆของท่านจะไม่ส่งผลกระทบต่อการรักษาของท่าน หรือความสัมพันธ์ต่อบุคลากรทางการแพทย์แต่ประการใด หากท่านเลือกที่จะไม่เข้าร่วม หรือถอนตัวออกจากการศึกษาวิจัย เรายังจะให้การรักษามาตรฐานที่ดีที่สุดกับท่านต่อไปแพทย์และผู้วิจัยมีสิทธิที่จะยุติการเข้าร่วมการศึกษาวิจัยนี้ของท่าน โดยไม่ต้องขอความยินยอมจากท่าน หากเห็นว่าเป็นการเหมาะสม ซึ่งรวมถึงการเกิดเหตุการณ์ไม่พึงประสงค์ การบาดเจ็บ หรือ อาการทางคลินิกของท่านอาจทำให้ท่านมีความเสี่ยงในการเกิดอาการแทรกซ้อนอย่างอื่น หรือด้วยเพราะเหตุผลอื่นๆ

ข้าพเจ้าได้อ่านและเข้าใจรายละเอียดในเอกสารนี้ครบถ้วนแล้ว

ลงชื่อ _____

วันที่_____

( )

APPENDIX C

GENERAL INFORMATION OF RESEARCH SUBJECT

เรื่อง: ผลของ *IrvingiaGabonensis*ต่อการควบคุมระดับน้ำตาลในเลือด และความไวต่ออินซูลินในผู้ที่มีระดับน้ำตาลในเลือดสูง

The effect of *IrvingiaGabonensis* on postprandial glycemic control and insulin sensitivity in pre-diabetic subjects

เลขที่แบบบันทึกข้อมูล_____HN_____

วันที่_____

ข้อมูลส่วนตัว

ชื่อ_____ นามสกุล_____

อายุ _____ ปีเพศ_____

อาชีพ_____

ที่อยู่_____

_____

เบอร์ติดต่อ_____

สถานภาพ ☐โสด ☐สมรส ☐หม้าย ☐หย่า

การศึกษา ☐มัธยม ☐ปวช/ปวส ☐ปริญญาตรี ☐สูงกว่าปริญญาตรี

ประวัติแพ้ ☐ไม่มี ☐มี ชื่อยา/อาหาร_____

อาการ_____

โรคประจำตัว ☐ไม่มี ☐มี ชื่อโรค_____

ได้รับการวินิจฉัยเมื่อ_____

การรักษา โดย_____

ยาใช้ประจำ ☐ไม่มี ☐มี ชื่อยา_____

ระยะเวลาการใช้_____

วิธีการใช้_____

ใช้ครั้งสุดท้ายเมื่อ_____

ประวัตครอบครัวที่ป่วยเป็นเบาหวาน ☐ไม่มี ☐มี

ประวัติโรคเบาหวานขณะตั้งครรภ์หรือมีประวัติคลอดลูกตัวโต (น้ำหนักตั้งแต่4กิโลกรัมขึ้นไป)

☐ไม่มี ☐มี

มีประวัติหรือเคยมีประวัติน้ำตาลในเลือดสูง (FPG 100-125 mg%หรือOGTT ≥140mg%)

☐ไม่มี ☐มี

ลักษณะการใช้ชีวิต และพฤติกรรมส่วนตัว

5. การรับประทานอาหาร
    1. จำนวนมื้อ / เวลา / ความตรงเวลา / ปริมาณ / มื้อพิเศษ

       _____

       _____
    2. ลักษณะใดที่ตรงกับพฤติกรรมการรับประทานอาหารของท่านมากที่สุด (คำนึงถึงสุขภาพเป็นหลัก / คำนึงถึงสุขภาพพอสมควร / ไม่คำนึงถึงสุขภาพเลย)

       _____
    3. ประเภทของอาหารที่รับประทานบ่อย

       _____
6. การดื่มน้ำและเครื่องดื่มแอลกอฮอล์
    1. น้ำเปล่า

       _____
    2. น้ำอัดลม

       _____
    3. เครื่องดื่มแอลกอฮอล์

       _____

       กรุณาระบุปริมาณต่อวัน หากเป็นน้ำอัดลมและเครื่องดื่มแอลกอฮอล์ให้ระบุความถี่ด้วย เช่น ดื่มน้ำอัดลม 1 ขวดต่อวัน ความถี่ประมาณ 4 วันต่อสัปดาห์

7. กิจกรรมทางกาย

    1. การใช้ชีวิตทั่ว ๆ ไปของท่านที่ไม่รวมถึงการออกกำลังกายอย่างจริงจังนั้นตรงกับลักษณะใดมากที่สุด (ออกแรงมาก / ออกแรงปานกลาง / แทบจะไม่ออกแรง)

    _____

    2. การออกกำลังกาย

    _____

    กรุณาระบุ ความถี่ ระยะเวลา ในการออกกำลังกายด้วย เช่น วิ่ง (30 นาที 1 วันต่อสัปดาห์) และเล่นฟุตบอล (1 ชั่วโมง 1 วันต่อสัปดาห์) เป็นต้น

8. การสูบบุหรี่

    1. ท่านสูบบุหรี่หรือไม่

    _____

    2. ท่านได้รับควันบุหรี่จากคนอื่นบ้างหรือไม่

    _____

    หากสูบบุหรี่ กรุณาระบุจำนวนมวนต่อวันด้วย

APPENDIX D

CASE RECORD FORM

The effect of *IrvingiaGaboenesis* on postprandial glycemic control and insulin sensitivity in pre-diabetic and non-diabetic subjects

PATIENT DETAILS:

Patient Initials | | | |

Patient Medical Record No. | | | | | | | | - | | |

Date of Birth

Date of Birth								
	Day		**Month**			**Year**		

Date of Informed Consent								
Day			**Month**			**Year**		

SCREENING

CO-MORBID CONDITIONS

Date of Assessment						
Date		Month			Year	

Has the patient had any history of the following events? (Please tick "✓")	No	Yes*	*If Yes, specify duration and details
Diabetes			
Hypertension			
Ischemic Heart Disease (IHD)			
Transient Ischemic Attack			
Cerebro vascular Accident			
Peripheral Vascular Disease			
Thrombosis of Vascular Access			
Liver disease			
Others, specify			

SCREENING

PHYSICAL EXAMINIATION

Date of Assessment							Temperature˚C			Route Code*	*Route codes A = Axillary O = Oral T = Tympanic R = Rectal
Date		Month			Year						
									●		

Resting blood pressure and heart rate to be taken after 5 minute sitting and prior to taking blood.

Body weight (kg)				#Blood Pressure (mm/Hg)		#Heart Rate (beats/min)
				systolic	diastolic	
		●				

Were any clinically significant abnormalities found? (please tick "✓")			
	NO	**YES***	***If yes, specified**
Head and Neck			
Ears/Eyes/Nose/ Throat			
Heart			
Lungs			
Abdomen			
Lymph. Nodes			
Extremities			
Neurologic			
Musculoskeletal			
Skin			
Other specify:			

COMPLETE BLOOD COUNT AT SCREENING

Assessment / Item / Units		Date of: Date		Month			Year	
Hematocrit	%							
Hemoglobin	g/dL							
Red Blood Cell Count	X 10^6 /µL							
Platelets	X 10^3 /µL							
White Blood Cell Count	X 10^3 /µL							

SCREENING

BLOOD CHEMISTRY AT SCREENING

Assessment / Item / Units		Date of: Date		Month		Year	
Glucose	mg/dL						
AST	U/L						
ALT	U/L						
Alkaline Phosphatase	U/L						
Blood Urea Nitrogen	mg/dL						
Serum Creatinine	mg/dL						

PATIENT ELIGIBITY – INCLUSION CRITERIA –

To be eligible for the study, patients must fulfill <u>ALL</u>of the following criteria:
(Please tick "✓")

	YES	**N**O
1) Male or female subjects aged between 30 – 60 years old		
2) No current active diseases of gastrointestinal tract, liver, kidney, allergy, diabetes, and AIDS.		
3) Participants are subjected to pass blood test of Blood Urea Nitrogen (BUN), serum creatinine, AST, ALT, ALP, fasting blood glucose, and complete blood count, physical examination and medical history record screening.		
4) All blood test results, except fasting blood glucose, should display value within the normal reference range. The fasting blood glucose has to less than the diagnostic diabetic level (126 mg/dL)		
5) Subjects voluntarily participate in the study and sign their names in consent forms		

PATIENT ELIGIBILITY – EXCLUSION CRITERIA

Patients who fulfill <u>ANY</u>of the following criteria are <u>not eligible</u> for the study:
(Please tick "✓")

	YES	NO
1. History of being allergic or intolerant to *IrvingiaGabonensis* products or derivatives		
2. History of diseases of gastrointestinal tract, liver, kidney, allergy, AIDS, and other diseases which may influence the bioavailability of *IrvingiaGabonensis*'s active compounds		
3. History of regular alcohol consumption or drug abuse		
4. History of regular smoking		
5. Subjects are under other medications a month prior to the study, particularly medications which alter the liver enzymes metabolism		
6. Subjects have participated in other clinical trial a month prior to the study		
7. Currently or previously (within 1 month) enrolled on other investigational drug trial(s).		

VISIT 1

TEMPERATURE

Date of Assessment							Temperature˚C			Route Code*	*Route codes A = Axillary O = Oral T = Tympanic R = Rectal
Date		Month			Year						
								●			

BLOOD PRESSURE, HEART RATE AND BODY WEIGHT

Resting blood pressure and heart rate to be taken after 5 minute sitting.

Date of Assessment					Blood Pressure (mmHg)				Heart rate (beats/min)	Body weight (kg)			
Date		Month		Year	systolic			diastolic					
												●	

TYPE OF BEVERAGE ADMINISTRATION

Date of Administration						
Date		Month			Year	

Type of Beverage		Volume Consumed
☐	*IrvingiaGabonensis*	
☐	Warm water	

GLUCOSE AND INSULIN LEVELS

Date of Administration						
Date		Month			Year	

Time point (min)	Glucose (mg/dL)	Insulin ( )
0		
30		
60		
90		
120		
150		

VISIT 2

TEMPERATURE

Date of Assessment							Temperature˚C			Route Code*	*Route codes A = Axillary O = Oral T = Tympanic R = Rectal
Date		Month		Year							
									●		

BLOOD PRESSURE, HEART RATE AND BODY WEIGHT

Resting blood pressure and heart rate to be taken after 5 minute sitting and prior to taking blood.

Date of Assessment						Blood Pressure (mmHg)		Heart rate (beats/min)	Body weight (kg)			
Date		Month		Year		systolic	diastolic					
											●	

TYPE OF BEVERAGE ADMINISTRATION

Date of Administration					
Date		Month		Year	

Type of Beverage		Volume Consumed
☐	*IrvingiaGabonensis*	
☐	Warm water	

GLUCOSE AND INSULIN LEVELS

Date of Administration						
Date		Month			Year	

Time point (min)	Glucose (mg/dL)	Insulin ( )
0		
30		
60		
90		
120		
150		

END OF STUDY

Date of end of study:

Date		Month			Year	

Enter main reason for patient ending study: ☐☐

(see codes below)

01. Patient completed study according to the protocol
02. Intolerable adverse event (Record on Adverse Event page)
03. Withdrawal requested *
04. Unrelated medical condition *
05. Administrative / Investigator decision *
06. Loss to follow-up *
07. Death on study (please complete 'Death Summary' page)
08. Other *

* Give details:

I have reviewed this case report form and I confirm that it is a true and accurate of this patient's history while on study.

Investigator's Signature _____ Date _____

WITHDRAWAL

Date of withdrawal:	Date		Month			Year	

Enter main reason for patient withdrawal: (see codes below)

02. Intolerable adverse event (Record on Adverse Event page)
03. Withdrawal requested *
04. Unrelated medical condition *
05. Administrative / Investigator decision *
06. Loss to follow-up *
07. Death on study (please complete 'Death Summary' page)
08. Other *

* Give details on End of Study page

Investigator's signature:_____ **Date:**_____

VISIT 1

แบบฟอร์มประเมินอาการไม่พึงประสงค์

□□□□□□□□						
□□		□□□			ปี	

Has the patient had any of the following events during the 8-hour period after the visit? Please provide score based on degree of severity (0 = none, 4 = severe) (Please tick "✓")

ในช่วงเวลา 8 ชั่วโมงหลังการทดสอบ ขอให้ท่านสังเกตอาการไม่พึงประสงค์ใดๆ ดังต่อไปนี้หรืออาการอื่นๆ ที่อาจจะเกิดขึ้น โดยให้ระดับความรุนแรงดังนี้

"0" ไม่มีอาการเลย

"1" มีอาการน้อย

"2" มีอาการอยู่บ้างแต่ไม่ส่งผลต่อการดำเนินชีวิตของท่าน

"3" มีอาการมาก โดยท่านสามารถทนต่ออาการนั้นได้ แต่ท่านรู้สึกว่าอาการนั้นส่งผลต่อการดำเนินชีวิตประจำวันของท่าน

"4" มีอาการชัดเจน โดยท่านไม่สามารถทนต่ออาการนั้นได้และทำให้ท่านไม่สามารถดำเนินชีวิตประจำวันได้ตามปกติ

กรุณาทำสัญลักษณ์ "✓" ในช่องให้คะแนน

	0	1	2	3	4	หมายเหตุ
ปวดศีรษะ						
รู้สึกอิ่ม						
มีอาการคัน						
รู้สึกถ่ายไม่สุด						
มีอาการคลื่นไส้						
รู้สึกมีลมมาก ผายลมบ่อย						
รู้สึกอ่อนล้า						
ท้องอืด						
ปวดท้อง						
อื่นๆ (โปรดระบุรายละเอียด)						

VISIT 2

แบบฟอร์มประเมินอาการไม่พึงประสงค์

					ปี	

Has the patient had any of the following events during the 8-hour period after the visit? Please provide score based on degree of severity (0 = none, 4 = severe) (Please tick "✓")

ในช่วงเวลา 8 ชั่วโมงหลังการทดสอบ ขอให้ท่านสังเกตอาการไม่พึงประสงค์ใดๆ ดังต่อไปนี้หรืออาการอื่นๆ ที่อาจจะเกิดขึ้น โดยให้ระดับความรุนแรงดังนี้

"0" ไม่มีอาการเลย

"1" มีอาการน้อย

"2" มีอาการอยู่บ้างแต่ไม่ส่งผลต่อการดำเนินชีวิตของท่าน

"3" มีอาการมาก โดยท่านสามารถทนต่ออาการนั้นได้ แต่ท่านรู้สึกว่าอาการนั้นส่งผลต่อการดำเนินชีวิตประจำวันของท่าน

"4" มีอาการชัดเจน โดยท่านไม่สามารถทนต่ออาการนั้นได้และทำให้ท่านไม่สามารถดำเนินชีวิตประจำวันได้ตามปกติ

กรุณาทำสัญลักษณ์ "✓" ในช่องให้คะแนน

	0	1	2	3	4	หมายเหตุ
ปวดศีรษะ						
รู้สึกอิ่ม						
มีอาการคัน						
รู้สึกถ่ายไม่สุด						
มีอาการคลื่นไส้						
รู้สึกมีลมมาก ผายลมบ่อย						
รู้สึกอ่อนล้า						
ท้องอืด						
ปวดท้อง						
อื่นๆ (โปรดระบุรายละเอียด)						

CURRICULUM VITAE

CURRICULUM VITAE

NAME	Mr. Anek Sony
DATE OF BIRTH	23 January 1984
ADDRESS	189/22 Lake View Park 1 Faham District, Chiang Mai, Thailand 50000

EDUCATIONAL BACKGROUND

2008	Doctor of Medicine Chiang Mai University

WORK EXPERIENCE

2013	Doctor Absolute Health Clinic
2012-2013	Doctor Stem Cell 21
2011-2012	Doctor Pleroma Aesthetic Clinic
2009-2011	Doctor Wuttisak Clinic
2008-2009	Doctor Lumpoon Hospital