

**A COMPARISON OF THE EFFICACY OF *SYZYGIUM JAMBOLANUM*
(JAVA PLUM) 6CH AND *SYZYGIUM JAMBOLANUM*
(JAVA PLUM) HOMOEOPATHIC MOTHER TINCTURE IN THE
TREATMENT OF TYPE 2 DIABETES MELLITUS IN PATIENTS ON
METFORMIN®**

PRETTY BRIGHTNESS MKHIZE

2016

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TYPE 2 DIABETES MELLITUS IN PATIENTS ON METFORMIN®**

**BY
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**Mini-dissertation submitted in partial compliance with the requirements of the
Master's Degree in Technology: Homoeopathy
In the Faculty of Health Sciences
Durban University of Technology
Durban**

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DECLARATION

This is to certify that the work is entirely my own and not of any other person, unless explicitly acknowledged (including citation of published and unpublished sources). The work has not previously been submitted in any form to the Durban University of Technology or to any other institution for assessment or for any other purpose.

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DEDICATION

I DEDICATE THIS WORK TO MY FATHER MARTIN MHLEZI MKHIZE (CHILLIES) AND MOTHER THOBILE JUDITH MKHIZE (MOTIVE). I WOULD NOT HAVE COMPLETED THIS JOURNEY WITHOUT YOUR UNFALTERING SUPPORT AND LOVE.

OKHABAZELA KaMAVOVO, GCWABE, GUBHELA, MUMB'OMHLOPHE, NINA BASEMBO NGIYABONGA ANGIPHEZI. I LOVE YOU.

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ABSTRACT

Background

Diabetes mellitus is a metabolic disorder with various aetiologies, characterised by hyperglycaemia, resulting from defects of carbohydrate, fat and protein metabolism due to the deficient action of insulin on target tissues caused by insensitivity to or lack of insulin or both. The long term effects of diabetes mellitus frequently include retinopathy, nephropathy and neuropathy and an increased risk of other diseases such as cardiac, peripheral arterial and cerebrovascular disease.

According to the International Diabetes Federation (IDF) 387 million people have diabetes mellitus and this number is predicted to rise to 592 million worldwide by 2035. In 2014 diabetes mellitus caused 4.9 million deaths worldwide and every 7 seconds a person dies from diabetes mellitus. The growing incidence of diabetes mellitus is a worldwide concern because of the increase of economic costs and burden of disease that is due to the cardiovascular complications and the co-morbidities.

Objective

The aim of this double-blind, randomised clinical trial was to determine the efficacy of *Syzygium jambolanum* (Java plum) 6CH and *Syzygium jambolanum* (Java plum) homoeopathic mother tincture on daily fasting blood glucose and glycosylated haemoglobin levels in type 2 diabetes mellitus patients on Metformin® in the treatment of type 2 diabetes mellitus.

Materials and Method

A sample consisted of 24 volunteers selected on the basis of inclusion and exclusion criteria. These participants were then randomly divided into two groups, 13 in the group receiving the homoeopathic potency and 11 in the group receiving the homoeopathic mother tincture. Each participant attended a total of five consultations with the researcher over a period of 14 weeks that included a 2 week baseline period followed by a 12 week treatment period, at the Durban University of Technology (DUT) or Kenneth Gardens Homoeopathic Day Clinic.

At each consultation a detailed and comprehensive homoeopathic case history (Appendix D) was taken and a physical examination (Appendix E) was performed by the researcher. Participants were required to fill in a log sheet (Appendix C1 and C2) with their fasting blood glucose readings daily for 14 weeks, which included a 2 week baseline period followed by a 12 week treatment period. Participants were also required to have their glycosylated haemoglobin measurements tested pre- and post-treatment.

Results

Both groups reflected a statistically significant reduction in fasting blood glucose levels as compared to the baseline. The mean fasting blood glucose level in week 1 was 11.8802 whereas in week 13 the mean blood glucose level was 8.6590 with a p value ≤ 0.05 for the *Syzygium jambolanum* 6CH group and the mean blood glucose level in week 1 was 9.0338 with a standard deviation of 1.2345 whereas in week 13 the mean blood glucose level was 6.8591 with a p value ≤ 0.05 in the *Syzygium jambolanum* homoeopathic mother tincture. However there was no significant differences between the two groups (*Syzygium jambolanum* 6CH and *Syzygium jambolanum* homoeopathic mother tincture), the significance score was 0.623 when comparing reduction in fasting blood glucose levels. Both groups reflected a statistically non-significant reduction in the glycosylated haemoglobin (HbA1C) and there were no significant differences between the two groups when comparing reduction in HbA1C levels.

Conclusion

Both homoeopathic preparations of *Syzygium jambolanum* (mother tincture and 6CH) significantly reduce fasting blood glucose levels in patients with type 2 diabetes mellitus. This result suggests that *Syzygium jambolanum* has beneficial anti-diabetic effects and warrants further investigation.

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DEFINITION OF TERMS

GAD65 Antibody

Glutamic acid decarboxylase (GAD) is a neuronal enzyme involved in the synthesis of the neurotransmitter gamma-aminobutyric acid (GABA). GAD65 antibody is also the major pancreatic islet antibody and an important serological marker of predisposition to type 1 diabetes. GAD65 autoantibody also serves as a marker of predisposition to other autoimmune disease that occur with type 1 diabetes, including thyroid disease (Mayo Clinic 2014).

Graves' disease

Graves' disease is an immune system disorder that results in the overproduction of thyroid hormones (hyperthyroidism). Although a number of disorders may result in hyperthyroidism, Graves' disease is a common cause (Mayo Clinic 2014).

Non-enzymatic glycation

Non-enzymatic glycation of proteins exposed to a hyperglycemic environment determines the formation of the advanced glycosylated end products (AGEs). RAGE (receptor for AGEs) are localized in the peripheral nerve, both the endothelial and the Schwann cells. Increased AGE levels contribute to the increased vascular permeability of diabetes (Shivashankara *et al.* 2013).

Oxidative stress

Oxidative stress contributes to the development of diabetic neuropathic complications through an increased production of reactive oxygen species and decreased endogenous capacity of neutralizing them. Oxidative Stress causes a series of changes in endothelial cell function and gene expression of genes. Oxidative stress increases the level of two vasogenic factors, endothelin-1 and angiotensin II which are potent vasoconstrictors and possible contributors to the reduced peripheral nerve blood flow (Shivashankara *et al.* 2013).

Protein kinase C

Protein kinase C includes a superfamily of isoenzymes, key players in intercellular signal transduction for hormones and cytokines. Hyperglycemia causes an increase in Protein kinase C activity which results in phosphorylation of intracellular proteins. Protein kinase C contributes to diabetic neuropathy by a neurovascular mechanism such as blood flow and conduction velocity (Shivashankara *et al.* 2013).

Polyol pathway abnormalities

In the presence of hyperglycemia, glucose enters the polyol pathway, the enzyme aldose-reductase using NADPH as a co-factor, catalyzes glucose to sorbitol therefore NADPH will no longer be available for synthesizing nitric oxide and glutathione. Then sorbitol dehydrogenase oxidizes sorbitol to fructose. The polyol pathway abnormalities result in an increase of intracellular sorbitol causes osmotic stress, fructose which is ten times more potent-glycated than glucose. Decrease in nitric oxide and glutathione (Shivashankara *et al.* 2013).

Pyogenic

An infection characterized by severe local inflammation, usually with pus formation, generally caused by one of the pyogenic bacteria (Mayo Clinic 2014).

Stocking glove Pattern

A pattern of peripheral nerve disease characterized by a relatively sharply demarcated loss of pain, touch, temperature, position and vibration sensation, accompanied by weakness, muscular atrophy, and loss of tendon reflexes-eg, the 'stocking' pattern of distal diabetic polyneuropathy (Medline Plus 2014).

Vasa nervorum endothelium

Blood vessels supplying nerves. Small vessels like vasa vasorum and vasa nervorum are particularly susceptible to external mechanical compression. Vasa nervorum and a decrease in blood flow through the vasa nervorum has been implicated in the development of diabetic neuropathy (Mayo Clinic 2014).

Xanthomas

Xanthomas are lipid deposits and are common, especially among older adults and people with high blood lipids. Xanthomas vary in size. Some are very small, others are bigger than 3 inches in diameter. They appear anywhere on the body, but are most often seen on the elbows, joints, tendons, knees, hands, feet, or buttocks. Xanthomas may be a sign of a medical condition that involves an increase in blood lipids. Such conditions include certain cancers, diabetes mellitus, Hyperlipidemia, Inherited metabolic disorders such as familial hypercholesterolemia, Primary biliary cirrhosis, Pancreatitis, Hypothyroidism (Medline Plus 2014).

CHAPTER 1: INTRODUCTION

1.1 INTRODUCTION

This double-blind randomised parallel clinical trial was conducted on two complementary medicine interventions for the treatment of type 2 diabetes mellitus.

1.2 PROBLEM STATEMENT

According to the International Diabetes Federation (IDF) 387 million people have diabetes mellitus, and it is predicted that this number will rise to 592 million worldwide by 2035. In 2014 diabetes mellitus caused 4.9 million deaths worldwide and every 7 seconds a person dies from diabetes mellitus. The growing incidence of diabetes mellitus is a worldwide concern because of the increase of economic costs and burden of disease that is due to the cardiovascular complications and the co-morbidities of diabetes mellitus (Canivell and Gomis 2014).

Diabetes mellitus affects people over the age of 60 years, however in the sub-Saharan African countries diabetes mellitus affects those who are within the economically productive age group of 30-45 years. The prevalence of diabetes mellitus in African communities is increasing due to the high urban growth rate, unhealthy dietary changes, physical inactivity and increasing obesity (Idemyor 2010). The long term complications of diabetes mellitus and the rising prevalence of diabetes mellitus in Africa will lead to economic and health system strain due to limited resources (Whiting, Hayes and Unwin 2003).

“Diabetes mellitus is a group of metabolic diseases characterised by hyperglycaemia which results from defects in insulin secretion, insulin action or both” (Selvin *et al.* 2011). Both environmental and genetic factors can cause an anomaly in the production of insulin, with the resulting deficiency in insulin causing abnormalities in carbohydrate, protein and lipid metabolism (Kuzuya *et al.* 2002). Diabetes mellitus is frequently associated with the development of microvascular and macrovascular diseases which

include nephropathy, retinopathy, neuropathy and cardiovascular diseases due to extended duration of abnormal diabetic metabolism (George, Augustine and Sebastian 2014).

The most common type of diabetes mellitus affecting children and young adolescents is type 1 diabetes mellitus. It has previously been referred to insulin-dependent diabetes or juvenile diabetes, it is increasing worldwide at the rate of 3-5% per year (Canivell and Gomis 2014). Type 1 diabetes mellitus is due to auto-immune destruction of insulin-producing beta cells in the pancreas which results in absolute insulin deficiency (Barrett 2013). The International Diabetes Federation (2014) estimated that more than 79 000 children were diagnosed with type 1 diabetes mellitus in the year 2013 worldwide (International Diabetes Federation 2014).

Type 2 diabetes mellitus is usually preceded by an asymptomatic stage termed as pre-diabetes where there is mild hyperglycaemia, insulin resistance and an early decrease in insulin secretion. With early lifestyle changes this risk stage can be managed (Inzucchi 2012).

Gestational diabetes mellitus is when glucose intolerance occurs for the first time during pregnancy. Glucose intolerance can cause adverse effects on the mother and infant if not treated (Kuzuya *et al.* 2002). More than 21 million live births were affected by diabetes mellitus during pregnancy in the year 2013 (International Diabetes Federation 2014)

This study attempted to illustrate homoeopathy as an adjunct in the management of type 2 diabetes mellitus and compare *Syzygium jambolanum* prepared in 6CH and homoeopathic mother tincture in order to investigate if one was more effective than the other.

Syzygium jambolanum has been a subject of research since it has been introduced in Europe in the 1880s. Although most reports rely on animal experiments, there is convincing evidence that parts of *Syzygium jambolanum* have anti-hyperglycaemic properties (Helmstädter 2008). *Syzygium jambolanum* is widely used to regulate blood sugar levels and may be used in diarrhoea or in any condition where a mild and

effective astringent is called for. The jambolanum tree is fast-growing and popularly occurs in areas bordering on the tropics and the very hot and humid places where there a wide range of environmental conditions (Helmstädter 2008).

Kohli and Singh (1993) reported a study on 30 patients with “uncomplicated” diabetes mellitus. Patients received 12 g *Syzygium jambolanum* seed powder in three divided doses for three months. An oral glucose tolerance test was performed every month and subjective parameters were monitored. There was a considerable and progressively increasing relief of symptoms such as polyuria, polyphagia, weakness and weight loss amongst others. Results of the glucose tolerance test were significantly improved after three months of treatment. Some studies reported increased glycogen content in liver and muscle cells (Kohli and Singh 1993).

In a different study the molecular mechanism of the anti-diabetic effects of homoeopathic preparations of *Syzygium jambolanum* and *Cephalandra indica* (mother tincture, 6CH and 30CH respectively) was undertaken in high fat and high fructose-induced type 2 diabetic rats. After 30 days of treatment, diabetic rats showed a significant decrease in serum insulin and lipid profile and it was concluded that *Syzygium jambolanum* and *Cephalandra indica* exhibit anti-diabetic effects by favouring glucose uptake and oxidation in skeletal muscle (Sampath *et al.* 2013).

To date no homoeopathic research has been conducted on humans to investigate the effect of *Syzygium jambolanum* in homoeopathic potency 6CH on the effect of blood glucose levels in type 2 diabetes mellitus.

This study is based on a study undertaken by Govender (2012) to determine the effect of *Momordica charantia* homoeopathic mother tincture and *Momordica charantia* 6CH on daily fasting blood glucose and glycosylated haemoglobin levels in type II diabetes mellitus patients on Metformin®. He concluded that both homoeopathic preparations of *Momordica charantia* (mother tincture and 6CH) did not significantly reduce fasting blood glucose or glycosylated haemoglobin levels in patients with type II diabetes mellitus on Metformin®. However, although his results were not statistically significant; there was a general reduction in fasting blood glucose levels evident in the data of both groups suggesting a degree of clinical significance which warranted further

investigation. Govender (2012) recommended that a study should be carried out over at least three months. This is because measuring of HbA1C at smaller intervals than three months contributed to the disparity between mean fasting blood glucose levels and mean HbA1C values recorded in his study (Govender 2012).

1.3 AIM OF THE STUDY

The aim of this double-blind, randomised clinical trial was to determine the efficacy of *Syzygium jambolanum* 6CH and *Syzygium jambolanum* homoeopathic mother tincture on daily fasting blood glucose and glycosylated haemoglobin levels in type 2 diabetes mellitus patients on Metformin®.

1.4 OBJECTIVES OF THE STUDY

1.4.1 The first objective

To determine the efficacy of *Syzygium jambolanum* (Java plum) 6CH in the treatment of type 2 diabetes mellitus.

1.4.2. The second objective

To determine the efficacy of *Syzygium jambolanum* (Java plum) homoeopathic mother tincture in the treatment of type 2 diabetes mellitus.

1.4.3 The third objective

To compare the efficacy of *Syzygium jambolanum* (Java plum) 6CH and *Syzygium jambolanum* (Java plum) homoeopathic mother tincture in the treatment of type 2 diabetes mellitus.

1.5 STATEMENT OF HYPOTHESIS

1.5.1 The first hypothesis

It is hypothesised that *Syzygium jambolanum* (Java plum) 6CH will be effective in reducing the fasting blood glucose and glycosylated haemoglobin levels in type II diabetes mellitus patients on Metformin®.

1.5.2 The second hypothesis

It is hypothesised that *Syzygium jambolanum* (Java plum) homoeopathic mother tincture will be effective in reducing the fasting blood glucose and glycosylated haemoglobin levels in type 2 diabetes mellitus patients on Metformin®.

1.6 NULL HYPOTHESIS

It is hypothesised that there will be no difference in effect between *Syzygium jambolanum* (Java plum) 6CH and *Syzygium jambolanum* (Java plum) homoeopathic mother tincture in reducing the fasting blood glucose and glycosylated haemoglobin levels in type 2 diabetes mellitus patients on Metformin®.

1.7 ASSUMPTIONS

- Participants regularly took their medication as prescribed.
- Participants did not change their lifestyle for the duration of the study.

CHAPTER 2: REVIEW OF RELATED LITERATURE

2.1 DIABETES MELLITUS

2.1.1 Definition

Diabetes mellitus is a metabolic disorder with various aetiologies, characterised by chronic hyperglycaemia. Chronic hyperglycaemia results from an irregularity in insulin secretion caused by the destruction of beta (β) cells of the pancreas and/or abnormalities of insulin action. Defects in the action of insulin cause disturbances in carbohydrate, fat and protein metabolism. There are several pathogenic mechanisms that are involved in the development of diabetes mellitus, such as the impairment or destruction of the pancreatic beta cells which consequently causes insulin deficiency, and other processes that cause resistance to insulin (American Diabetes Association 2013).

Characteristic symptoms of marked hyperglycaemia include polydipsia, polyuria, weight loss, polyphagia, blurred vision, susceptibility to certain infections and sometimes an impairment of growth. People with diabetes are often diagnosed with other diseases that affects the cardiac system as well as peripheral arterial and cerebrovascular systems. Severe clinical manifestations such as ketoacidosis, non-ketotic hyperosmolar states and hypoglycaemia can result in the absence of treatment (American Diabetes Association 2013).

2.2 INCIDENCE AND EPIDEMIOLOGY

A vast number premature deaths and disabilities worldwide are due to non-communicable diseases. In 2011 diabetes mellitus accounted for an estimated 4.6 million deaths worldwide, more than HIV and malaria combined (International Diabetes Federation 2014).

Guariguata *et al.* (2014) conducted a literature based study that aimed to estimate global prevalence of diabetes mellitus for 2013, as well as projections for 2035. Their literature search included PubMed, Medline, and Google Scholar, and targeted research conducted from January 1980 through April 2013 and including data sources reporting the age-specific prevalence of diabetes. Altogether 744 data sources were identified representing 162 countries, of which 174 were selected representing 130 countries. Guariguata *et al.* (2014) showed that an estimate of 381.8 million adults in 130 countries and territories were diagnosed with diabetes in the year 2013; and projected a possible rise to 591.9 million by the year of 2035 (Guariguata *et al.* 2014).

Diabetes mellitus affects people worldwide and whilst it seems to be well controlled in well-developed countries, this is not the case in sub-Saharan countries. This is due to a rise of infectious diseases such as HIV/AIDS, tuberculosis and malaria that contribute to a continual high death rate. This therefore causes a double disease burden in the low socioeconomic countries which face scarce financial resources and poses a challenge to the health care systems (Idemyor 2010).

Late diagnosis of diabetes and poor health care leads to early presentation of diabetic complications affecting the economically productive age group in sub-Saharan Africa (Idemyor 2010).

The International Diabetes Federation (IDF) Atlas estimated that about 11 million individuals in the sub-Saharan Africa have diabetes, and future projections estimated a possible rise to at least 19 million diabetes mellitus sufferers by the year 2025, this reflects the enormous health problem posed by diabetes in this region (International Diabetes Federation 2014).

South Africa has a diverse population with an estimated total of 50.6 million, with 79% of people classified as black, 9% as coloured, 9% as white and 2.5% as Indian/Asian. It is estimated that the prevalence of type 2 diabetes mellitus is about 5.5% for people older than 30 years of age (Amod *et al.* 2012). According to Amod *et al.* (2012) the prevalence of type II diabetes mellitus and the development of complications is not equal in the different ethnic groups of South Africa and is as follows:

- Indian/Asian descents have the highest risk of 17.1% and seem to be at higher risk from a younger age, about 10 years earlier than other ethnic groups.
- Urbanised black risk is 6.4%, with the risk in females older than 60 increasing to 16.7%.
- White risk is 6.2%.
- Coloured risk is 6.2%, increasing after 60 years of age to 25.3%, with females having a prevalence of 33.3%.

The growing prevalence of diabetes mellitus amongst the black and coloured females is highly attributed to obesity, with the prevalence of obesity in coloured women being 26.3% and in black females 31.8% as compared to the 21.1% prevalence of white females. There is a poor correlation between obesity and diabetes in the Indian/ Asian ethnic group in South Africa (Amod *et al.* 2012).

It is recommended that people of Indian descent should be screened for type 2 diabetes mellitus at an earlier age and more frequently than other ethnic groups and that all colored and black females should be screened at an age of 40 years especially if their body mass index is raised (Amod *et al.* 2012).

2.3 CLASSIFICATION OF DIABETES MELLITUS

The American Diabetes Association (2013) classifies diabetes into four major categories:

- Type 1 diabetes mellitus.
- Type 2 diabetes mellitus.
- Gestational diabetes.
- Other specific diabetes.

2.3.1 Type 1 diabetes mellitus

Type 1 diabetes mellitus results from a cellular mediated autoimmune destruction of the beta cells (β -cells) of the pancreas and accounts for 5-10% of diabetes mellitus cases. It was previously known by the terms 'insulin-dependent diabetes' or 'juvenile onset diabetes' (Van Belle, Coppieters and Von Herrath 2011).

Autoimmune destruction of beta cells involves both genetic predisposition and environmental factors. Eighty five percent to ninety percent of individuals diagnosed with type 1 diabetes mellitus present with one or two antibodies which are markers of the immune destruction of the beta cells of the pancreas. Markers of the immune destruction of beta cells include islets cell antibodies, auto-antibodies to insulin, antibodies to GAD (GAD 65) and antibodies to the tyrosine phosphatases IA. Some patients, whilst lacking the evidence of beta cell autoimmunity still have permanent insulopaenia without known cause and are prone to episodic ketoacidosis (Van Belle, Coppieters and Von Herrath 2011).

The rate of beta cell destruction is quite variable, being rapid in infants and children (generally presenting as ketoacidosis) and slow in adults where there is residual beta cell function sufficient to prevent ketoacidosis, although mild hyperglycaemia may be present, eventually leading to severe hyperglycaemia and/or ketoacidosis during infections and stress. Patients diagnosed with type 1 diabetes mellitus are prone to ketoacidosis, coma and even death as well as other autoimmune disorders such as Graves' disease, Hashimoto's thyroiditis, Addisons disease, vitiligo, celiac sprue, autoimmune hepatitis, myasthenia gravis and pernicious anaemia (American Diabetes Association 2013).

2.3.2 Type 2 diabetes mellitus

Type 2 diabetes mellitus previously known by the terms 'non-insulin diabetes mellitus' or 'adult-onset diabetes', accounts for 90-95% of diabetes mellitus cases (American Diabetes Association 2013).

Specific causes of type 2 diabetes mellitus are unknown and autoimmune destruction of beta cells in the pancreas does not occur although insulin resistance and relative insulin deficiency are common aspects. Obesity or abdominal obesity is common in patients diagnosed with type 2 diabetes mellitus which causes some degree of insulin resistance (Stumvoll, Goldstein, and van Haeften 2005).

This form of Diabetes mellitus may go undiagnosed for years because of gradual mild hyperglycaemia in the earlier stages and the lack of classic diabetic symptoms. There is a high risk of developing type 2 diabetes mellitus as one increases with age, obesity, physical inactivity and gestational diabetes mellitus (Stumvoll, Goldstein and van Haeften 2005).

2.3.3 Gestational diabetes mellitus

Initially gestational diabetes mellitus was defined as a degree of glucose intolerance which occurs at the onset of or during pregnancy. However, this definition presented certain limitations because in some cases the diabetes resolved with delivery. This definition never considered that unrecognised glucose intolerance can begin concomitantly with pregnancy (Setji, Brown and Feinglos 2005).

Different associations such as the International Association of the Diabetes and Pregnancy Study Groups (IADPSG), an international consensus group with representatives from multiple obstetrical and diabetes organisations including the American Diabetes Association (ADA), endorsed that women who presented with diabetes at their first prenatal visit be diagnosed with type 2 diabetes mellitus rather than gestational diabetes mellitus (American Diabetes Association 2013).

2.3.4 Other specific types

2.3.4.1 Genetic defects of beta cells

This is a form of diabetes that occurs because of monogenetic defects in beta cell function which results in impaired insulin secretion with minimal or no defect in insulin action. Characteristically there is an early onset of hyperglycaemia generally before the age of 25 years also referred to as maturity-onset diabetes of the young (Hattersley and Ashcroft 2005).

2.3.4.2 Genetic defects in insulin action

This is a form of diabetes that results from genetically determined abnormalities of insulin action which leads to hyperinsulinaemia. Signs and symptoms are variable and may range from mild hyperglycaemia to severe hyperglycaemia. Some may present with acanthosis nigricans, and women may be infertile and have enlarged cystic ovaries which was previously known as 'type A insulin resistance' (Goodarzi Dumesic, Chazenbalk and Azziz 2011).

Leprechaunism and the Rabson-Mendenhall syndrome are two pediatric syndromes. They both have mutations in the insulin receptor gene which results in alterations in insulin receptor function and extreme insulin resistance. Leprechaunism syndrome has characteristic facial features and is usually fatal in infancy, whilst the Rabson-Mendenhall syndrome is associated with abnormalities of teeth and nails and pineal gland hyperplasia (Goodarzi, Dumesic, Chazenbalk and Azziz 2011).

2.3.4.3 Disease of exocrine pancreas

Any process that can cause diffuse injury to the pancreas can cause diabetes. Conditions such as pancreatitis, trauma, infection, pancreatectomy, pancreatic carcinoma and haematochromatosis can cause reduction in beta cell mass and extensive pancreatic fibrosis and calcification (Hardt *et al.* 2000). Patients may experience abdominal pain radiating to the back due to fibrocalculous pancreatopathy. Pancreatic calcifications can be identified on X-ray examination. Pancreatic fibrosis

and calcium stones in the exocrine ducts can also be seen on autopsy (Hardt *et al.* 2000).

2.3.4.4 Endocrinopathies

Hormones such as glucagon, growth hormone, cortisol and epinephrine counteract the actions of insulin. An excess amount of these hormones can predispose one to diabetes mellitus, especially in individuals with insulin secretion defects, and hyperglycaemia. This can resolve when the hormone excess is resolved (Al-Agha *et al.* 2011; Jerreat 2010).

2.3.4.5 Drug or chemical induced diabetes

Many drugs such as nicotinic acid and glucocorticoids can precipitate diabetes by impairing insulin action especially in patients with severe insulin resistance. Certain drugs such as Vacor (rat poison) and intravenous pentimide can permanently destroy the beta cells (Craig, Hattersley and Donaghue 2009).

2.3.4.6 Infection induced diabetes

Certain viruses such as those causing congenital rubella have been associated with beta cell destruction, although type 1 autoimmune antibodies are also present. Coxsackievirus B, cytomegalovirus, adenovirus, and mumps have been implicated in inducing certain cases of the disease (Filippi and von Herrath 2005).

2.3.4.7 Uncommon forms of immune mediated diabetes

There are numerous anti-insulin receptor antibodies that can cause diabetes, some antibodies can bind to the insulin receptor which prevents the binding of insulin, to its receptor in target tissues causing severe insulin resistance. These are frequently found in patients diagnosed with systemic lupus erythematosus and other autoimmune diseases. On the other hand some antibodies can act as an insulin agonist by binding

to the receptor causing hypoglycaemia. This syndrome was previously referred to 'type B insulin resistance (Pihoker *et al.* 2005).

Majority of 'stiff-man syndrome' sufferers will develop diabetes mellitus. 'Stiff-man syndrome' sufferers experience stiffness of the axial muscles coupled with with painful spasms because it is an autoimmune disorder affecting the central nervous system with high levels of glutamic acid decarboxylase (GAD) autoantibodies. (Pihoker, Gilliam, Hampe and Lernmark 2005).

2.3.4.8 Other genetic syndromes sometimes associated with diabetes

There is an increased risk of developing diabetes mellitus with many genetic syndromes, this is attributed by chromosomal abnormalities of Down syndrome, Klinefelter syndrome, and Turner syndrome. Wolfram syndrome presents with the lack of beta cells at autopsy which is the attributing factor for the insulin-deficient diabetes. (Seino *et al.* 2010).

2.5 RISK FACTORS OF DIABETES MELLITUS

Type 2 diabetes mellitus has become prevalent because of aging, increased incidence of abdominal visceral obesity, physical inactivity, and urbanisation (American Diabetes Association 2013).

2.5.1 Age

The International Diabetes Federation estimates that the peak age for onset of diabetes in 2010 was 40-59 years, but by 2030, the highest prevalence will be in the age-group of 60-79 years. In the sub-Saharan countries, diabetes mellitus peaks at the age of 55-64. As the diabetes pandemic grows diabetes mellitus onset will shift to a younger age group indicating an earlier onset (Mbanya, *et al.* 2010).

2.5.2 Urbanisation

Sub-Saharan Africa has the fastest urbanisation rate worldwide with more than a third of the population living in urban areas, a figure predicted to increase to 45% by 2025. This rapid urbanisation in the region is suggested to be the major cause of the rising burden of diabetes and other cardiovascular diseases (Mbanya, Motala *et al.* 2010). The movement of population from rural to urban areas is associated with major changes in lifestyle in particular with an increased availability of high calorie foods and drinks (Amod *et al.* 2012). Obesity prevalence is also due to urbanisation because of its association with modernisation of cultures and stress (Ng *et al.* 2014).

About a century ago only 20% of the world population lived in cities and in the least developed countries such as Africa the percentage was only 5. It is estimated that over half the world population live in urban cities and 40% of the African population now live in in urban cities and it is expected to rise to 56% in the year 2050 (Neiderud 2015).

2.5.3 Obesity

Obesity is an abnormal or excessive accumulation of fat to such an extent that it impairs health. The adverse consequences of obesity include insulin resistance, type II diabetes mellitus, dyslipidaemia, hypertension, coronary heart disease, hyperuricemia, osteoarthritis and malignancies of the breast, endometrium and colon (Ng *et al.* 2014).

Obesity has doubled since 1980. In 2014 13% of the world's adults (18 years or older) and 42 million children under the age of 5 were classified as obese. South Africa has the highest rate of obesity amongst adults in the sub-Saharan Africa, with 42% of women and 39% of men being obese (Gill *et al.* 2009).

Adipocytes are not only fat-storing cells, but are also metabolically active, secreting leptin, growth factors and cytokines. When adiposity increases – especially abdominal visceral fat – insulin sensitivity decreases (Amod *et al.* 2012).

2.5.4 Physical inactivity

Urbanisation in sub-Saharan Africa has caused an increase in the westernised lifestyle which is characterised by physical inactivity and increased consumption of high-fat or energy-dense diets (Mbanya *et al.* 2010).

Physical inactivity is related to obesity. The development of insulin resistance is either directly or through weight gain linked to physical inactivity (Nagi 2005).

2.6 ANATOMY AND PHYSIOLOGY OF THE PANCREAS

The pancreas is a soft, elongated grayish pink gland that lies retroperitoneally and transversely across the posterior abdominal wall in the epigastric and hypochondriac regions of the body. In adults the pancreas is 12-20 cm long and weighs 70-120 g (Renius and Simon 2014).

The pancreas is divided into four parts, namely the head, neck, body and tail. The common bile duct enters the head of the pancreas posteriorly, passing through the parenchyma before joining the main pancreatic duct to empty into the small intestine through the major duodenal papilla (Renius and Simon 2014) (Figure 1).

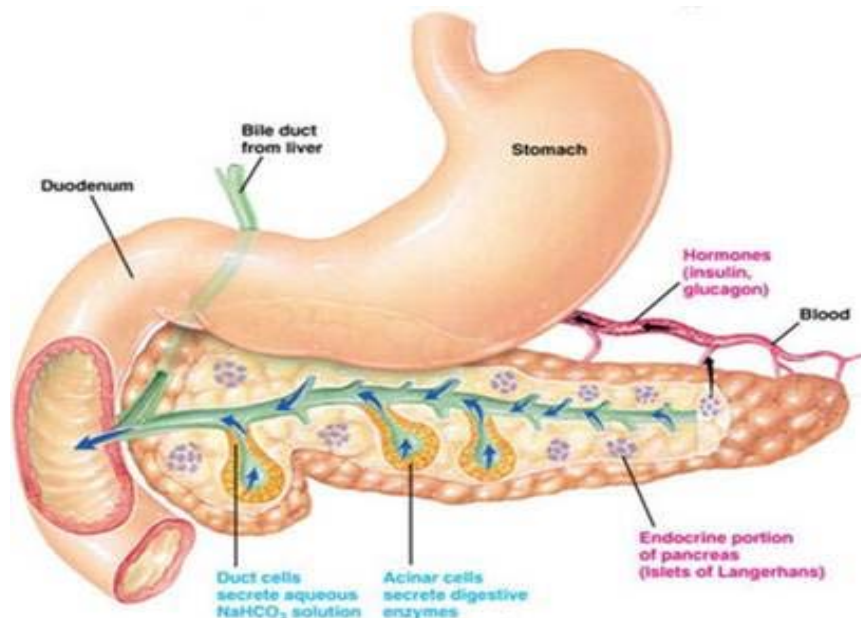


Figure 1: The pancreas. (The Pancreas 2015).

The pancreas is a mixed gland, consisting of both exocrine and endocrine tissue. The exocrine tissue responsible for the secretion of digestive enzymes and alkaline pancreatic juice makes up 80-90% of the pancreas, with the remaining 2% of the pancreas consisting of the endocrine cells grouped in collections called the Islets of Langerhans or pancreatic islets. The Islets of Langerhans secrete the hormones insulin, glucagon, somatostatin and pancreatic polypeptide directly into the blood (Kumar *et al.* 2007).

The Islets of Langerhans are ovoid and scattered throughout the pancreas. Humans have 1-2 million islets. Pancreatic islets have 4 endocrine secreting cells (Whitehead and Miell 2013):

- Alpha cells make up 20% of the islets and secrete glucagon.
- Beta cells are the most common cell type, accounting for 60-75% of the islets and generally being located in the center of each islet. Beta cells secrete insulin.
- Delta cells secrete somatostatin.
- F-cells secrete pancreatic polypeptide.

2.7 GLUCOSE REGULATION

Blood glucose concentration is maintained within a range of 4-8 mmol/L by the interaction of a number of hormones. Insulin and glucagon are the hormones that interact to regulate blood glucose concentrations by negative feedback (Colledge *et al.* 2006).

2.7.1 Insulin

Insulin was first described by Banting and Best in the year 1922. Insulin is a polypeptide molecule consisting of a 21-amino acid α -chain joined to 30-amino acid β -chain. Insulin release is directly regulated by blood glucose levels (Davies, Blakeley and Kidd 2001).

Insulin is an anabolic hormone primarily responsible for preventing the persistence of raised levels of glucose in the blood; it achieves this by promoting the uptake of glucose and other nutrients into the liver, muscle and fat (Whitehead and Miell 2013).

Whilst cells use glucose as an energy substrate, some such as liver, central nervous system, red blood cells and kidneys are independent of insulin, whilst others such as skeletal muscle, cardiac muscle and adipose tissue depend on insulin to transport glucose into the cells. When insulin is absent, those tissues that depend on insulin switch to using free fatty acids as an energy substrate, resulting in the accumulation of ketones and other acids leading to metabolic acidosis (Davies, Blakeley and Kidd 2001).

2.7.2 Glucagon

Glucagon's primary role is the elevation of blood glucose. It is a catabolic hormone, stimulating the breakdown of glycogen into glucose in the liver and also stimulating gluconeogenesis (Whitehead and Miell 2013).

Hypoglycaemia is the main stimulus for glucagon release. Other amino acids such as arginine and alanine have been shown to stimulate secretion (Davies, Blakeley and Kidd 2001).

2.7.3 Normal glucose physiology

Normal glucose homeostasis is regulated by three interrelated processes because glucose is always present in the body and it is continually replaced and removed to maintain a relative constant concentration of 5 mmol/l (Colledge *et al.* 2006).

1. Glucose production in the liver.

Low blood glucose levels (hypoglycaemia) stimulate the secretion of glucagon from the alpha cells of the pancreatic islets. Glucagon acts on hepatocytes to accelerate the conversion of glycogen into glucose (glycogenolysis) and promotes the formation of glucose from lactic acid and certain amino acids (gluconeogenesis). As a result hepatocytes release glucose into the blood thus raising the blood glucose level (Tortora and Derrickson 2011).

2. Glucose uptake and utilisation by peripheral tissue, mainly the skeletal muscles by the action of insulin.

If blood glucose continues to rise, high blood glucose inhibits release of glucagon via negative feedback. High blood glucose (hyperglycaemia) stimulates secretion of insulin by the beta cells of the pancreatic islets. Insulin acts on various cells in the body to accelerate facilitated diffusion of glucose into cells, especially into skeletal muscle fibers, and to speed up the conversion of glucose into glycogen (glycogenesis) or fatty acids (lipogenesis). In addition, insulin will increase the uptake of amino acids by cells and their synthesis into protein, slow down the conversion of glycogen to glucose (glycogenolysis) and slow the formation of glucose from lactic acid and amino acids (gluconeogenesis). As a result blood glucose levels fall (Colledge *et al.* 2006).

3. Counter regulatory hormones such as glucagon.

If blood glucose level drops below normal, low blood glucose inhibits release of insulin (negative feedback) and stimulates release of glucagon (Colledge *et al.* 2006).

Although blood glucose level is the most important regulator of insulin and glucagon, several hormones and neurotransmitters also regulate the release of these two hormones. Human growth hormone and adrenocorticotrophic hormone (ACTH) indirectly stimulate secretion of insulin because they act to elevate blood glucose (Colledge *et al.* 2006).

2.8 PATHOGENESIS OF TYPE 2 DIABETES MELLITUS

Type 2 diabetes mellitus is a complex endocrine and metabolic disorder, there are two metabolic defects that are characteristic in Type 2 diabetes mellitus (Kumar *et al.* 2007):

1. A decreased ability of peripheral tissue to respond to insulin; and
2. Impaired pancreatic beta cell dysfunction.

Although diabetes is multifactorial in aetiology, certain genetic predispositions and different environmental influences converge to cause insulin resistance which results in compensatory beta cell hyperplasia to maintain normoglycaemia.

Premature beta cell dysfunction is due to the increase demand of insulin due to insulin resistance (Unger 2012).

Type 2 diabetes mellitus does not develop until the beta cells fail to compensate for the insulin resistance state. Eventually beta cell secretory dysfunction sets in, resulting in impaired glucose tolerance and leading to chronic hyperglycaemia which results in diabetes mellitus (Unger 2012).

2.9 CLINICAL FEATURES OF TYPE 2 DIABETES MELLITUS

Hyperglycaemia causes a wide variety of symptoms. The classical symptoms as outlined by the American Diabetes Association (2013) include thirst, dry mouth, polyuria, nocturia and loss of weight. However, many patients may present with non-specific complaints such as chronic fatigue and malaise or even be asymptomatic. Other symptoms include hyperphagia with a predilection for sweet foods, mood change, irritability, difficulty in concentration and apathy.

Uncontrolled diabetes mellitus is associated with an increased susceptibility to infection such as skin sepsis (boils), pruritus vulvae in females and balanitis in males which can be an indication of genital candidiasis (Bakhru 2006).

Hypertension is present in at least 50% of patients with type 2 diabetes mellitus. Hyperlipidemia is common but xanthelasma and eruptive xanthomas are rare (Amod *et al.* 2012).

2.10 DIAGNOSIS

Criteria for the diagnosis of type 2 diabetes is as follows (American Diabetes Association 2013):

- A1C \geq 6.5%. The test should be performed in a laboratory using a method that is NGSP (National Glycohaemoglobin Standardisation Program) certified and standardised to the DCCT (Diabetes Control and Complication Trial) assay.*

OR

- Fasting Plasma Glucose ≥ 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*

OR

- Two-hour plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during an Oral Glucose Tolerance Test. The test should be performed as described by the World Health Organisation, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

OR

- In a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L).

*In the absence of unequivocal hyperglycaemia, criteria 1–3 should be confirmed by repeat testing.

2.10.1 Urine Tests

2.10.1.1 Glucose

Checking for glucose levels in urine is a common procedure, using sensitive glucose-specific dipsticks. Testing should be performed on urine passed 1-2 hours after a meal. Glycosuria always warrants further assessment by blood testing. However, it must be remembered that there are numerous benign conditions that may cause glycosuria which is unrelated to diabetes. These include pregnancy, gastric surgery, hyperthyroidism, peptic ulceration and hepatic diseases (Sacks *et al.* 2011).

2.10.1.2 Ketones

Ketones in the urine do not entirely suggest diagnoses of diabetes mellitus unless associated with glycosuria. Ketonuria can also occur in people who have been exercising strenuously for long periods, who have been fasting, people who have been on a high fat low carbohydrate diet and been vomiting repeatedly. Ketones can be easily observed in plasma using dipsticks. (Jung and Park 2012).

2.10.1.3 Protein

To detect the existence of renal disease or urinary infection in people with diabetes a standard procedure of testing for albumin using the dipstick is used. Vigorous exercise, fever, heart failure, menstruation, and prostatitis can also cause increased protein in urine (Jha *et al.* 2010).

2.10.2 Blood Tests

2.10.2.1 Glycosylated haemoglobin (HbA1C)

The glycosylated haemoglobin test measures the percentage of blood glucose attached to haemoglobin. The higher the sugar levels the more the haemoglobin is attached with glucose (Dogra *et al.* 2015).

Glycosylated haemoglobin is a widely used marker, reflecting the average blood glucose over a 2-3 month period. Expert committees have recently recommended the use of glycosylated haemoglobin for the diagnosis of diabetes mellitus due to the highly standardised A1C assays and the many established and emerging studies of A1C (WHO 2011).

The American Diabetes Association supports the use of glycosylated haemoglobin for the diagnosis of diabetes mellitus recommending a threshold of A1C \geq 6.5%. The diagnostic test should be performed using a method certified by the National Glycohaemoglobin Standardisation Program (NGSP) and standardised to the

Diabetes Control and Complication Trial reference (DCCT) (American Diabetes Association 2013).

The glycosylated haemoglobin test is superior to the fasting plasma glucose test because it is convenient since fasting is not required and is more accurate in periods of stress and illnesses. Glycosylated haemoglobin is more costly with limited availability in certain regions of developing countries. Certain conditions such as anaemia and haemoglobinopathies that cause abnormal red cell turnover can be misleading in the diagnosis and management of diabetes mellitus (Koga and Kasayama 2010).

Glycosylated haemoglobin is used to assess the glycaemic control in a patient with known diabetes mellitus and plays a critical role in the management of diabetes mellitus (American Diabetes Association 2013). Patients diagnosed with type 2 diabetes mellitus with HbA1C level > 7.5% have a 2.5 to 5 fold greater chance of developing microvascular complications and a fivefold greater risk of developing peripheral artery disease (Amod *et al.* 2012).

An HbA1C target of < 7% is recommended in the majority of diabetic patients and a HbA1C target of < 6.5% in newly diabetes diagnosed patients and those without cardiovascular disease is recommended. An HbA1C target of < 7.5% in the elderly and those of limited life expectancy is accepted (Amod *et al.* 2012).

2.10.2.2 Fasting plasma glucose

Fasting plasma glucose is the testing of glucose after a fast. If glucose is the only test required an 8 hour fast is sufficient whilst if other tests are assayed along with glucose a 12 hour fast is recommended. During the interval of fasting no foods or drinks other than water are allowed (Dods 2013).

The normal range for FPG is usually 3.9-5.5 mmol/L (70-100 mg/dL). A range of 5.6-6.9 mmol/L (100-125 mg/dL) is indicative of the prediabetes stage often accompanied with mild diabetic complications of microalbuminuria and cardiovascular risk therefore

early detection is important so as to treat complications. A level \geq than 7 mmol (126 mg/dL) is indicative of diabetes mellitus (Scobie and Samaras 2012).

2.10.2.3 Oral glucose tolerance test

The oral glucose tolerance test (OGTT) focuses on a two-hour glucose response following a 75 g oral glucose load. A two-hour plasma glucose level \geq 11.1 mmol/L (200 mg/dL) indicates a positive test for diabetes mellitus. The OGTT is a good provocation test for early detection of diabetes in patients whose fasting glucose falls short of diagnostic ranges and for patients considered at risk (Scobie and Samaras 2012).

2.11 COMPLICATIONS OF TYPE 2 DIABETES MELLITUS

The incidence and prevalence of diabetes mellitus has continued and increased globally especially in the poorer developing countries. People with type 2 diabetes mellitus are more vulnerable to varied forms of both short (acute) term and long term complications because of the insidious onset and therefore the late recognition of this form of the disease (Amod *et al.* 2012).

Undetected, untreated or poorly controlled diabetes mellitus can lead to devastating complications and premature death (Amod *et al.* 2012).

2.11.1 Short/Acute complications

2.11.1.1 Diabetic ketoacidosis

Diabetic ketoacidosis occurs when the body is unable to produce enough insulin. Insulin plays a key role in helping the body process the glucose which is the main energy source for muscles and other tissue. The body breaks down fat for energy therefore producing ketones which are dangerous acids that can lead to seizures, coma and death. The body excretes ketones in urine and acetone via exhalation which causes a fruity odour on the breath. Ketoacidosis quantifies urgent medical attention because of the detrimental effects (Katsilambros *et al.* 2011).

The mortality rate of diabetic ketoacidosis has decreased considerably in the developed world but it still prevalent in South Africa. Diabetic ketoacidosis is a frequent cause of admission to hospital. In South Africa the mortality rate is between 6.8-9% whilst in the developed countries, the mortality rate is < 1%. Diabetic ketoacidosis is an important condition that requires correct recognition and management (Amod *et al.* 2012).

Symptoms of diabetic ketoacidosis (Jerreat 2010):

- Nausea, vomiting;
- Tiredness and weakness;
- Abdominal pain;
- Heavy breathing, acetone odour;
- Pain in the chest or side, respiratory distress; and
- Unconsciousness, diabetes coma

2.11.1.2 Hyperosmolar hyperglycaemia non-ketotic syndrome

The hyperglycaemic hyperosmolar state is characterised by the slow development of marked hyperglycaemia, hyper molality and severe dehydration. The classical picture of hyperosmolar hyperglycaemia state includes a history of polyuria, polydipsia, vomiting, dehydration, weight loss, weakness and a change in the mental status. The mental status can vary from mild confusion to profound lethargy or coma. Focal neurological signs and seizures may also occur (Scobie and Samaras 2012).

2.11.1.3 Hypoglycaemia

Hypoglycaemia is a common complication in diabetes mellitus especially on individuals using insulin or insulin secretagogue (e.g. sulphonylurea). Hypoglycaemia may manifest during sleep. Hypoglycaemia in diabetes mellitus occurs when the plasma glucose falls to < 4.0 mmol/l. In mild hypoglycaemia patients should be treated immediately by eating or drinking a simple sugar such as a glucose sweet or sugary cold drink followed by a sandwich or other form of carbohydrate. If left untreated, this condition can become severe and lead to unconsciousness (Frier 2007).

Symptoms include irritability, numbness in the arms and hands, sweating, confusion, headaches, extreme hunger, shakiness or dizziness (American Diabetes Association 2013). Severe hypoglycaemia may cause permanent neurological damage or brain death, and may be responsible for sudden death related to cardiac arrhythmia (Amod *et al.* 2012). Recent trials from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) have demonstrated a clear relationship between hypoglycaemia and the risk of cardiovascular mortality. The risk of cardiovascular death was increased by 1.4-3.7 fold in patients who had had a recent hypoglycaemic episode (Bonds *et al.* 2010).

2.11.2 Long term complications

There are a number of pathological changes that occur as diabetes mellitus progresses over the years. These changes largely involve the vascular system and sometimes the skin and lens of the eye. Patients with diabetes mellitus are also prone to certain types of infections. Diabetic vascular diseases affect both the small (microvascular) and large (macrovascular) blood vessels (Masharani, Karam and German 2007).

2.11.2.1 Microvascular complications

Microvascular complications are a result of disease in smaller blood vessels. These changes can affect the retina (whitehead) resulting in ophthalmologic complications, the kidney resulting in renal complications and the nervous system causing neurological complications. Diabetic microvascular damage is characterised by microthrombosis, hyperpermeability and angiogenesis (Nakao and Hata 2012).

2.11.2.1.1 Ophthalmologic complications

2.11.2.1.1.1 Diabetic retinopathy

Diabetic retinopathy affects up to 40% of patients with diabetes with 8% having sight-threatening retinopathy. Diabetic Retinopathy is the leading cause of visual impairment

in diabetes mellitus. Diabetic retinopathy is preventable and treatable with smoking cessation, optimal glycaemic and blood pressure control (Hariprasad *et al.* 2007).

The eye is a light receptor and therefore consists of a minimal network of blood vessels which could disturb the transparency of the eye. The minimal network of blood is required to meet with the demand of blood supply of the eye, but leaves the eye vulnerable to hypoxia. The oxygen demand for the eye is higher than any other central neuronal systems (e.g. the brain) because dark adaptation needs much oxygen (Nakao and Hata 2012).

There are two main categories of diabetic retinopathy referred to as proliferative retinopathy and non-proliferative retinopathy (Mohamed, Gillies and Wong 2007):

2.11.2.1.1.1 Non-proliferative retinopathy

Non-proliferative retinopathy occurs in the early stages of diabetic retinopathy, where the retinal capillaries leak protein, lipids or red cells into the retina in the area of the macula causing macular edema. As the macula contains a concentration of visual cells there will be interference with visual acuity causing visual impairment (Dods 2013). Non-proliferative diabetic retinopathy is characterised by microaneurysms, haemorrhages, venous bleeding, capillary loss and intraretinal microvascular abnormalities (Mohamed, Gillies and Wong 2007).

2.11.2.1.1.2 Proliferative retinopathy

Proliferative retinopathy which may occur at the optic disc or elsewhere on the retina occurs as a result of small blood vessel occlusion which stimulates new capillary growths and fibrous tissue formation. Before the growth of new capillaries, a pre-proliferative phase of arteriolar ischaemia occurs which manifests as cotton wool spots (small infarcted areas of the retina). Severe visual loss only occurs when vitreous haemorrhage or retinal damage occurs (Mohamed, Gillies and Wong 2007).

2.11.2.1.1.2 Cataracts

There are two types of cataracts that occur in diabetic patients, namely, subscapular cataract and senile cataract (Nakao and Hata 2012).

2.11.2.1.1.2.1 Subscapular cataract

Develops below the lens capsule, having a flocculent or snowflake appearance. This normally occurs in type 1 diabetes mellitus and progresses fairly rapidly. It is directly linked with the hyperglycaemia of uncontrolled diabetes mellitus (Obrosova, Chung and Kador 2010).

2.11.2.1.1.2.2 Senile cataract

This is a common type of cataract in both non-diabetic and diabetic patients although it tends to occur at a younger age in diabetic patients with poor glycaemic control. This type of cataract occurs as a result of sclerotic changes of the lens nucleus (Nakao and Hata 2012).

Hyperglycaemia causes two independent abnormalities in senile cataract. These are glycosylation of the lens protein as well as sorbitol accumulation which causes osmotic changes in the lens that lead to fibrosis and cataract formation (Nakao and Hata 2012).

2.11.2.1.1.3 Glaucoma

Glaucoma, although uncommon, results from neovascularisation in certain cases after cataract extraction, where there is an accelerated growth of new blood vessels obstructing outflow of the aqueous fluid (Shoshani *et al.* 2012).

2.11.2.2 Renal complications

2.11.2.2.1 Diabetic nephropathy

Diabetic nephropathy is the most common cause of end-stage renal disease in both type 1 and type 2 diabetes mellitus, causing high mortality and disability rates in patients with diabetes. Twenty five to forty percent of patients diagnosed with diabetes mellitus develop nephropathy within 20-25 years of diagnosis (Amod *et al.* 2012). Chronic hyperglycaemia is the direct stimulus for the release of cytokines and growth factors which are toxic to renal tubules. Proteinuria is the first manifestation that occurs as kidney function declines and urea and creatinine accumulate. Diabetic nephropathy is characterised by the thickening of the capillary basement membranes and of the mesangium of renal glomeruli causing glomerulosclerosis and renal insufficiency (Tervaert *et al.* 2010).

2.11.2.3 Neurological complications

Peripheral and autonomic neuropathy are the most common diabetic neuropathies in both type 1 and type 2 diabetes mellitus with about 50% of type 2 diabetic patients being affected (Tesfaye and Selvarajah 2012).

2.11.2.3.1 Peripheral neuropathy

Chronic hyperglycaemia is a major initiator of diabetic peripheral neuropathy. Hyperglycaemia affects numerous pathogenic mechanisms, causing abnormalities in polyol pathway, non-enzymatic glycation, activation of protein kinase c and oxidative stress, and this results in the dysfunction of the vasa nervorum endothelium. The vasa nervorum subsequently decreases nerve blood flow causing hypoxia and damage to the nerves (Shivashankara *et al.* 2013).

Peripheral neuropathy includes both distal symmetric polyneuropathy and isolated peripheral neuropathy. Distal symmetric polyneuropathy is the most common form of diabetic peripheral neuropathy. It affects mainly the longer nerves hence the impact on the foot. A stocking-glove pattern is observed because of an axonal neuropathic

process delaying both the motor and sensory nerve conduction. The sensory peripheral nerves are usually the first to be affected with associated symptoms such as a dulled perception on vibration and temperature. Pain can vary from a mild discomfort to severe incapacitating symptoms although when there is a sufficient degree of sensory loss, pain perception is diminished resulting in unperceived neuropathic injury. Motor peripheral nerves are affected later, with the lack of innervation to the small muscles of the foot resulting in clawing of the toes and displacement of the submetatarsal fat pads. Such changes can affect biomechanics of the foot, increasing plantar pressures. A combination of these processes can lead to calluses and ulcerations (Tesfaye and Selvarajah 2012). Foot problems are a major cause of morbidity and mortality in people with diabetes mellitus, and contribute to increased healthcare costs (Amod *et al.* 2012). Peripheral neuropathy predisposes the development of Charcot arthropathy, a condition that presents acutely with pain and swelling and if left untreated can cause a rocker bottom deformity and ulceration (Dyck *et al.* 2011).

Isolated peripheral neuropathy is a process where one nerve (mononeuropathy) or several nerves are affected (mononeuropathy multiplex) followed characteristically by a recovery of all or most of the function. It tends to affect cranial nerves and femoral nerves and motor abnormalities are common (Kluding *et al.* 2012). Cranial nerve three (oculomotor), four (trochlear) and six (abducens) which all innervate the eye usually show weakness upon examination, whilst the pupil is spared. Cranial nerve involvement presents with diplopia. In cases where the femoral nerve is affected, diabetic amyotrophy occurs, resulting in severe pain in the front of the thigh, together with wasting and weakness of the quadriceps (Canal *et al.* 2013).

2.11.2.3.2 Autonomic neuropathy

Autonomic neuropathies are common in patients with long-standing diabetes mellitus, affecting various visceral functions such as blood pressure and pulse, gastrointestinal activity, bladder functions and erectile function. Nausea, vomiting, postprandial fullness, reflux, dysphagia and constipation are amongst the common symptoms experienced when the autonomic neuropathies affect the gastrointestinal system.

Diabetic erectile dysfunction due to neuropathy is usually persistent and accompanied by urinary incontinence (Dey and Attele 2011; Deli *et al.* 2013).

2.11.2.4 Cardiovascular complications

The risk of developing cardiovascular complications is higher in type 2 diabetic patients compared to non-diabetics, with women being 4-5 times more susceptible and males being 2-3 times more susceptible (Amod *et al.* 2012). Arteriosclerosis is the main cause of cardiovascular complications, and the chronic hyperglycaemia and hyperdyslipidaemia associated with diabetes are risk factors for the formation of atherosclerosis. Atherosclerosis decreases the blood supply to tissues, causing ischaemia and infarctions to end organs. Heart diseases are commonly due to myocardial infarcts and congestive myopathies (Whitehead and Miell 2013).

Diabetes mellitus is also an important strong independent risk factor for strokes (Nannetti *et al.* 2009). Stroke affects more than 700,000 individuals each year; it is the third largest cause of death and the largest cause of adult disability worldwide (Air and Kissela 2010).

Peripheral vascular diseases include ischaemia of the lower extremities, impotence and intestinal angina. Marked atherosclerosis is accelerated in the larger arteries and in certain areas of turbulent blood flow such as at the bifurcation of the aorta. Patients diagnosed with type 2 diabetes mellitus are 30 times more prone to develop gangrene on their feet than non-diabetics because of peripheral vascular disease resulting in peripheral neuropathies associated with the loss of pain sensations. Gangrene can result in ulcerations and amputations (Amod *et al.* 2012).

2.11.2.5 Skin Infection and mucous membrane complications

Patients who are diabetic are prone to several unusual infections which are often a result of ischaemia from atherosclerosis and peripheral vascular diseases. Chronic pyogenic, candidial infections, vulvovaginitis with persistent glycosuria and eruptive xanthomas associated with hypertriglyceridemia are common in chronically uncontrolled diabetes mellitus (Behm *et al.* 2012).

2.11.2.6 Bone and Joint Complications

Larkin *et al.* (2014) describes three different bone and joint complications which are a result of the metabolic and vascular sequel of long standing diabetes mellitus.

2.11.2.6.1 Diabetic cheiroarthropathy

This is a chronic progressive syndrome that causes stiffness of the hand resulting from contracture and tightening of the skin over the joints. This occurs in poor glycaemic controlled diabetics because of the glycosylation of collagen and other proteins in connective tissue. Characteristically one is unable to flatten the palm against a flat surface (commonly known as 'prayer sign' (Cherqaoui, McKenzie and Nunlee-Bland 2013).

2.11.2.6.2 Dupuytren contractures

This is a condition that can occur in non-diabetics but is more common in diabetic patients. Characteristically there is nodular thickening and contracture of the palmer fascia that causes flexure contractures of the fingers (Zyaluk and Puchalski 2015).

2.11.2.6.3 Carpal tunnel syndrome

Carpal tunnel syndrome occurs when the median nerve is compressed. It is more common in people with long standing diabetes mellitus and results from the glycosylation of collagen and other proteins in the connective tissue (Colomb-Lippa and Wilson 2011).

Adhesive capsulitis, increased bone fractures, hyperuricaemia and gout are common diseases in long standing diabetes which is associated with obesity, hypertension and dyslipidaemia (Larkin *et al.* 2014).

2.11.2.7 Depression

Clinical depression or major depression disorder is more prevalent in diabetics than in non-diabetics. Clinical features usually include a depressed mood with diminished interest, loss of energy and concentration difficulties. This is associated with the threat of complications, self-management demands, unsupported interrelated personal relationships (Gonzalez, Fisher and Polonsky 2011). Depression is thought to be the consequence of disease because of the burden of chronic illness which causes a negative impact on life quality, function disability and reduced lifespan (Renn, Feliciano and Segal 2011). Papelbaum, Moreira *et al.* investigated the association between depression and glycaemic control in type 2 diabetes. Seventy patients with type 2 diabetes mellitus were evaluated and underwent psychiatric examination; results showed that 13 patients were depressed out of the 70 (18.6%) and had increased levels of glycosylated haemoglobin when compared to the others who did not exhibit a mood disorder. The study concluded that the presence of depression seems to impact short term control of type 2 diabetes mellitus (Papelbaum *et al.* 2011) A study examined the association of diabetes and the onset of depression by reviewing the literature and conducting a meta-analysis of longitudinal studies on this topic. All studies published by EMBASE, Medline and PsycInfo that examined the relationship between type 2 diabetes mellitus and onset of depression were assessed. Eleven studies met the inclusion and exclusion criteria. The authors concluded from the data collected that people with type 2 diabetes mellitus have a 24% increased risk of developing depression (Nouwen *et al.* 2010).

2.12 MANAGEMENT OF TYPE 2 DIABETES MELLITUS

Early detection of those at risk for the development of diabetes mellitus together with implementation of early intervention strategies such as diet, exercise and medication can prevent the progression of diabetes mellitus and its associated complications (Amod *et al.* 2012). Both the Finnish Diabetes Prevention study and the Chinese Da Qing study have concluded that type 2 diabetes mellitus can be prevented by making changes in the diet such as promoting moderate weight loss and increasing the level of physical activity (Amod *et al.* 2012).

2.12.1 Education

Diabetes self-management education is the cornerstone for achieving a successful health care outcome for individuals with diabetes mellitus. Education promotes compliance to certain strategies in an effort to lifestyle changes (Haas *et al.* 2013).

2.12.2 Nutrition

A healthier lifestyle of reducing calorie intake, consuming less trans fats, cholesterol, saturated fats, and sodium is encouraged in individuals diagnosed with type 2 diabetes mellitus that is associated with obesity. Amongst many therapeutic interventions this is the most important one (Heisler *et al.* 2005; Zipp *et al.* 2011).

The Idaho Plate method is a healthy meal planning tool and is helpful for managing both diabetes mellitus and losing weight. Patients are able to choose the foods they enjoy but within recommended portion sizes. The plate method encourages patients to increase portions of non-starchy vegetables and decrease the portion size of starches this will assist with glucose control (Jumawan 2011).

2.12.3 Physical activity

Randomised, controlled trials have concluded that dietary changes combined with physical activity can delay the progression of impaired glucose tolerance to type 2 diabetes mellitus. Regular physical activity and cardiorespiratory fitness reduces cardiovascular risk factors, improves glycaemic control significantly and improves symptoms of depression (Zanuso *et al.* 2010).

People with type 2 diabetes mellitus are encouraged to perform at least 150 minutes per week of moderate-intensity aerobic physical activity combined with resistance training three times a week. Numerous benefits arise in regular physical activity such as maintenance of weight loss, improved glycaemic control, improved lipid profile, decreased insulin resistance improved blood pressure, reduced abdominal and overall fat percentage, improved well-being, decreased anxiety and stress (Look Ahead Research Group 2015).

2.12.4 Self-monitoring of blood glucose

Self-monitoring has changed diabetes care by providing diabetic individuals with the ability to measure their own blood glucose levels at any time. Diabetics can use the information of their blood glucose levels appropriately resulting in improved overall glycaemic control (Austin *et al.* 2006). Chronic hyperglycaemia significantly increases the risk for long term microvascular and macrovascular complications of diabetes therefore glycaemic control reduces the risk of such complications (Amod *et al.* 2012). An open label randomised pilot trial set to estimate the efficacy of a self-monitoring based disease management strategy in patients with type 2 diabetes mellitus treated with oral agent monotherapy was conducted by Franciosi *et al.* (2011). Participants were randomly selected into the self-monitoring management strategy or usual care group. Results showed that after six months there was a significant reduction in mean glycosylated levels and weight in the self-monitoring group compared with the control group. It was further concluded that self-monitoring improves metabolic control.

2.12.5 Allopathic treatment

2.12.5.1 Biguanide (Metformin®)

Metformin® is a plant extract, isolated from *Galega officinalis* (goats rue), which was initially used to treat symptoms characteristic of diabetes mellitus in the medieval times but was found to be toxic in the early 1920s. Metformin® was then developed in the 1950s and is now well known and well established as the primary 'anchor' oral anti-diabetic agent in the management of type 2 diabetes mellitus. Metformin® is the initial therapy of choice and should be started at the time of diagnosis in all patients whether overweight or normal weight (Bailey and Turner 1996).

Metformin® is the only drug that has proven efficacy in reducing cardiovascular outcomes and mortality. When Metformin® is used as monotherapy, it can reduce glycosylated haemoglobin (HbA1C) by 1-2%. Metformin® reduces hepatic glucose production by activating adenosine monophosphate kinase, improves insulin sensitivity to improve glucose utilisation, reduces gastrointestinal glucose absorption, improves free fatty metabolism, lipid profiles and enhances incretin responses (Eurich *et al.* 2005). It is the only diabetic allopathic drug that reduces circulating insulin and does not cause weight gain nor does it cause hypoglycaemic episodes when used in monotherapy (Rena, Pearson and Sakamoto 2013).

About 30% of those using Metformin® will report gastrointestinal side-effects such as diarrhoea, cramping, bloating and flatulence. Lactic acidosis with Metformin® is rare and only occurs in cases of inappropriate usage (Eurich *et al.* 2005).

2.15.5.2 Sulphonylureas

Sulphonylurea drugs have been used in the treatment of type 2 diabetes mellitus since the 1950s. Sulphonylureas induce insulin release by binding to specific pancreatic beta-cell channel receptors (Rendell 2004).

The United Kingdom Prospective Diabetes Study concluded that sulphonylureas can cause a reduction of the glycosylated haemoglobin from 1.5-2% and significant reduction in microvascular complications (Smith, Fisher and McKay 2010).

2.15.5.3 Alpha glucosidase inhibitors

Acarbose is an oligosaccharide that inhibits alpha glucosidase on the brush border of the small intestine, therefore inhibiting the conversion of complex carbohydrates into monosaccharides, resulting in a reduction and delay in the absorption of glucose (Van de Laar *et al.* 2006). Gastrointestinal side-effects such as diarrhoea and flatulence are common with alpha glucosidase inhibitors. The adverse gastrointestinal side effects are related to the fermentation of the high saccharide load in the colon. Discontinuation rates are as high as 35% due to side effects in clinical trials. When used as monotherapy, Arcabose does not cause hypoglycaemia but can aggravate hypoglycaemia if used in conjunction with sulphonylureas and insulin (Van de Laar *et al.* 2006).

2.15.5.4 Incretins

2.15.5.4.1 Dipeptyl peptidase-4 inhibitor (DPP-4)

The DPP-4 inhibitors appear to reduce HbA1c by 0.55-1.15% when compared to placebo groups. Short term studies (6-24 months) have proven that DPP-4 inhibitors have a good safety profile especially when used as monotherapy as compared to that of placebo groups. It is safe to use in the elderly without dose adjustment (Drucker and Nauck 2006).

DPP-4 inhibitors do not cause weight gain or hypoglycaemia unless used in combination with drugs capable of causing hypoglycaemia, although certain adverse effects can occur such as nasopharyngitis, urinary tract infection, lymphopenia, pancreatitis and hypersensitivity skin reaction (Umpierrez and Meneghini 2013).

2.15.5.4.2 GLP-1 agonists

GLP-1 agonists act as incretins, which are hormones that are secreted in the gut by enteroendocrine cells within minutes after eating. This hormone increases insulin secretion from beta cells and suppresses glucagon secretion from alpha cells resulting in an increase of insulin-mediated glucose in peripheral tissue and suppression of hepatic glucose production, both of which result in lowering blood glucose (Campbell 2011).

Exenatide and liraglutide are examples of GLP-1 agonists. Weight loss associated with these two drugs was measured in the LEAD-6 study which compared exenatide 10ug and liraglutide 1.8mg taken twice daily. The mean weight loss over 26 weeks was about 3kgs and the HbA1c reduction was 1.1% with liraglutide verses 0.8% with exenatide. Liraglutide is said to be more potent than exenatide in reducing fasting glucose (Yoon *et al.* 2009).

The most common side effect of GLP-1 agonists are nausea and vomiting which occur during initial therapy and in most cases this can be quite severe, even leading to discontinuation of the drug. Recent reports have reported that GLP-1 agonists can cause pancreatitis and are therefore contra-indicated if patient has a history of, or potential for, pancreatic disorders (Umpierrez and Meneghini 2013).

2.15.5.5 Thiazolidinediones

Both rosiglitazone and pioglitazone are thiazolidinediones which are indicated for the treatment of type 2 diabetes mellitus either as monotherapy or in combination with Metformin®, sulphonylureas and insulin. Thiazolidinediones are drugs that increase the sensitivity of insulin through multiple mechanisms, such as alterations in fatty acid uptake and in adipokine release (Consoli and Formoso 2013).

Both rosiglitazone and pioglitazone have a modest effect on glycaemic control and in maximum doses lower the HbA1c by 1-1.5%. Both can also increase high-density lipoprotein (HDL) by approximately 10% and pioglitazone has a neutral effect on low-

density lipoprotein (LDL) whilst rosiglitazone increases LDL cholesterol (Kahn and McGraw 2010).

2.15.5.6 Insulin

All varieties of insulin that are used in South Africa are produced by using recombinant DNA technology and have the same molecular structure as naturally produced human insulin. The insulins differ in duration of action, preservatives and additives for buffering and retarding. An individual insulin regimen has been formulated for each patient and this regimen should mimic the normal blood insulin levels as closely as possible (Nolan, Damn and Prentki 2011).

The insulins that are used in South Africa are the ultra-fast insulin acting analogues with an almost immediate onset of action which are normally administered subcutaneously 30 minutes before meals, and usually used in combination with the longer acting insulins for control of diabetes. The bi-phasic insulin preparations which are ready mixed preparations of a short-acting and intermediate acting insulin are useful in patients with poor vision and the elderly. Due to the fact that insulin is administered in the form of subcutaneous injections, hypertrophy of fat tissue may occur at the sites of injection. In very rare cases an allergic reaction has been reported (Inzucchi 2012).

2.12.6 Nutritional supplements

Nutritional supplements are commonly used in diabetics which not only help control blood sugar levels but also reduce end organ damage and may provide many additional benefits (Dey and Attele 2011).

2.12.6.1 Alpha lipoic acid

Alpha lipoic acid is a sulfur-containing antioxidant which is derived from octanoic acid. Alpha lipoic acid is a powerful antioxidant and plays a key role in the regulation of blood sugar by directly influencing insulin levels and stimulating the uptake of glucose in the peripheral tissues by regulating molecules that encourage the uptake of glucose

uptake by skeletal muscle cells, cardiomyocytes and adipocytes. Alpha lipoic acid reduces symptoms of diabetic polyneuropathy in the feet and legs. Alpha lipoic acid prevents many of the pathological changes associated with diabetic retinopathy and reverses late stage oxidative stress that is associated with many of the diabetic complications (Shay *et al.* 2009).

2.16.6.2 Omega-3 fatty acids

Omega-3 fatty acids are a large group of essential, unsaturated fats that include EPA (eicosapentaenoic acid), ALA (Alpha lipoic acid) and DHA (docosahexaenoic acid). Omega-3 fatty acids decrease the incidence of macrovascular injury, preserves renal function and to a lesser extent reduces inflammation of pancreatic beta cells. The DHA significantly reduces damage to the rod and cone cells of the retina (Massey 2013).

2.12.6.3 Chromium

In small amounts chromium is essentially important for human health and it is believed it helps increase glucose transport into the tissues and directly binds to insulin, this makes the insulin more stable and prolonged. Chromium also prevents glycosylation and oxidative stress in red blood cells and monocytes under hyperglycaemic conditions (Juturu and Gormley 2012).

2.12.6.4 Vitamin D

Vitamin D is not a vitamin but a hormone that has numerous benefits for the cardiovascular, immune, gastrointestinal and nervous system. Vitamin D reduces the risk of developing diabetes; lower levels of Vitamin D are associated with a greater risk of developing pre-diabetes. Vitamin D plays a role in reducing diabetes related end organ damage (Takiishi *et al.* 2010).

2.12.7 Phytotherapy

Phytotherapy is the term used to describe the therapeutic application of herbal medicines and was first described by the French physician Henri Leclerc (1870-1955). Phytotherapy is one of the oldest forms of medicine. Most races, religions and cultures use plants to sustain life and alter the course of the disease. Herbal medicine or phytomedicine is the science and art of using botanical medicines to prevent and treat illnesses. Phytomedicine is finding it difficult to make progress in its fight for recognition as a scientific discipline because of the vast range of indications of plants without validation from controlled clinical trials (Heinrich *et al.* 2012).

In contrast to pharmaceutical drugs which are based on single molecules that may or may not be derived from natural substances, herbal medicines are chemically complex and may contain many different phytochemicals such as tannins, isoflavones, saponins, flavonoids, glycosides that are often responsible for the therapeutic properties of herbal medicine. The intra-herbal interactions of the plant constituents are suspected give herbs a broad therapeutic range and good tolerability (Heinrich *et al.* 2012).

Phytotherapy is not homoeopathy although many confuse it and may use both terms interchangeably. Homoeopathy uses plants in fundamentally different ways from those of phytotherapy, and uses other substances besides plants (Bone and Mills 2013).

2.12.7.1 Fennugreek (*Trigonella foenum*)

Fennugreek (*Trigonella foenum*) is one of the oldest medicinal plants which originated in India and North Africa. Fennugreek is known to reduce sugar loss in urine and improve the glucose tolerance test (Gunn, Che and Farnsworth 2013). Fennugreek is a soluble fiber which slows down gastric emptying therefore delaying glucose absorption. Fennugreek also raises the rate of insulin release and increases insulin sensitivity (Kotsirilos, Vitetta and Sali 2011). Sharma *et al.* (1996) studied the glycaemic effects of fennugeek seed powder in 60 patients diagnosed with type 2 diabetes mellitus. Patients took 25 g of fenugreek seed powder divided into 2 doses at lunch and supper. The researchers concluded that fenugreek reduces blood glucose

levels and significantly decreases glycosylated haemoglobin however insulin levels are not affected (Sharma *et al.* 1996).

2.12.7.2 Bitter Melon (*Momordica charantia*)

Bitter melon (*Momordica charantia*) grows in tropical areas in East Africa, Asia and in the Caribbean. It is cultivated in South America as a common food for use in cooking and medicine, and is well known for its hypoglycaemic and anti-bacterial properties as well as its digestive aid in intestinal gas, bloating and stomach ache. Bitter melon contains several insulin-like polypeptides and substances that lower glucose levels and increase insulin sensitivity (Kotsirilos, Vitetta and Sali 2011).

2.12.7.3 Cinnamon (*Cinnamomum cassia*)

Cinnamon is rich in chalcone polymers which increase the insulin receptor-mediated signaling and activity of kinases, thus improving blood glucose (Kiec-Wilk *et al.* 2013). Cinnamon improves triglycerides, HDL and LDL levels and can potentially play a role as a dietary supplement. Cinnamon contains chromium and polyneols which are beneficial in lowering blood glucose (Kotsirilos, Vitetta and Sali 2011). A double-blind clinical trial was conducted on 44 patients with type 2 diabetes mellitus to evaluate the glycaemic and lipid effect of cinnamon, results showed a significant decrease of fasting blood glucose, glycosylated haemoglobin levels, triglycerides, weight, body mass index and concluded cinnamon may have a moderate effect in improving glycaemic status indicators (Vafa *et al.* 2012).

2.12.7.4 *Gymnema sylvestre*

Gymnema sylvestre is a plant native to India and widely used in the treatment diabetes mellitus and obesity. The chewing of *Gymnema* leaves reduces cravings for sweets things. *Gymnema sylvestre* contains a group of compounds known as gymnemic acids that play a role in the anti-diabetic effects of the plant by improving glucose uptake and utilisation (Massey 2013). A single blind randomised clinical trial was

conducted on patients diagnosed with type 2 diabetes mellitus who took 500mg of *Gymnema sylvestre* twice daily for a period of three months. Results showed reductions of polyphagia, fatigue, blood glucose and glycosylated haemoglobin and concluded *Gymnema sylvestre* has beneficial effects in the management of diabetes mellitus (Kumar, Mani and Mani 2010).

2.12.7.5 Garlic (*Allium sativum*)

Allium sativum is a well-known herb commonly used worldwide for flavor and spice. It has diverse advantageous biological properties such as its anti-diabetic, anti-carcinogenic, anti-arteriosclerosis and anti-thrombosis effects. *Allium sativum* has been shown to improve glycaemic control by increasing insulin sensitivity, glucose tolerance, and insulin secretion and also improves glucose utilisation in the skeletal muscles. *Allium sativum* has anti-oxidant properties which are useful regressing the development of diabetes. Side-effects include breath and body odour, heartburn and allergic reactions when used as raw garlic (Badole, Ghule and Wagh 2013). A double blind clinical trial was conducted to evaluate the potential hypoglycaemic effects of garlic in type 2 diabetic patients. Sixty patients completed the study; 30 patients ingested 300g of garlic three times daily and 30 patients ingested Metformin® twice daily. Results showed a significant reduction in fasting glucose at 24 weeks as compared to the placebo group. It was concluded that garlic may be a good addition in the management of type 2 diabetes mellitus (Jelodar *et al.* 2005) .

2.12.7.6 Ginseng (*Panax quinquefolius*)

The extract of ginseng root has been shown to decrease postprandial glycaemia and improve fasting blood glucose and HbA1c after 8 weeks of use (Kotsirilios, Vitetta and Sali 2011). Korean and American ginseng contain sulfonylurea-like activity (Kiec-Wilk *et al.* 2013). Vuksen *et al.* performed a randomised double-blind clinical trial on 19 participants with well controlled type 2 diabetes mellitus to evaluate the glycaemic efficacy of ginseng. Two grams of ginseng was administrated for 12 weeks and the researchers concluded ginseng maintained good glycaemic levels and improved plasma glucose and plasma insulin regulation beyond usual therapy in people with well-controlled type 2 diabetes mellitus (Vuksan *et al.* 2000).

2.12.7.7 *Morinda lucida benth*

The leaves of this plant are traditionally used in Nigeria and the root is used in Cameroon for a condition described as uncontrolled diuresis with similar symptoms to diabetes (Gunn, Che and Fransworth 2013). A methonal extract of the *Morinda lucida benth* leaves was given to normal and streptozotocin-induced hyperglycaemic rats and it was demonstrated that it lowered fasting blood glucose levels therefore demonstrating that *Morinda lucida benth* has antihyperglycaemic and hypoglycaemic properties (Adeneye and Agbajie 2008).

2.12.8 Homoeopathy

Homoeopathy was founded by a German physician Dr. Samuel Hahnemann (1755-1843). Homoeopathy is a medical science that is based on the principle 'Similia Similibus Curantur', meaning 'like cures like', any substance that can produce symptoms in a healthy person can cure those same symptoms in a sick person (Gray 2000). Homoeopathy is holistic taking a broad view of illness, cause of disease and the ways in which people express their illness individually. Homoeopathy treats the whole person (physical, mental, emotional) and the remedies assist people to regain health by stimulating their natural forces (Owen, Leckridge and Fisher 2007).

Hahnemann said "The highest ideal of cure is rapid, gentle and permanent restoration of the health or removal annihilation of the disease in it whole extent, in the shortest most reliable and most harmless way, on easily comprehensive principles" (Hahnemann 1996). Homoeopaths believe that cure is the restoration of health and not merely removal of symptoms of parts affected and symptoms should move in a specific direction ('The law of cure'), from vital organs to less vital organs, from within outward, from above downwards and in reverse order of appearance (Roberts 2002).

The fundamentals of homoeopathy are based on the principles of Simplex, Similimum and Minimum. 'Simplex' means simple medicines not compounds should be prescribed and encompasses the Law of Single Remedy which is practiced in classical homoeopathy, where the patient is given one remedy at a time simply because when the remedy is tested, it was tested singly. 'Similimum' means when the totality of

symptoms of the patient is taken, it will yield a picture that corresponds to one medicine which encompasses the Law of Similars which states that the more exact the match between the symptoms the remedy can cause, and the symptoms now produced by the disturbed vital force, the greater ability of the remedy to resonate with the sick person and affect their health. 'Minimum' means a low dosage of medicine is recommended. In homoeopathy less is more encompassing the Law of Minimum dose: "The quantity of action to affect any changes in nature is the least possible, decisive amount is always minimum and infinitesimal" (Hahnemann, 1996).

A homoeopathic potency is the measure of the power of the medicine based on the degree to which it has been potentised, expressed in terms of the degree of dilution. Homoeopathic remedies at any potency are products that have been prepared in accordance with a homeopathic manufacturing procedure as defined by the German Pharmacopoeia or recognised national homeopathic pharmacopoeias (Roberts 2005).

Potentisation is a mathematico-mechanical processing of a substance for the reduction of the crude, inert or poisonous medical state to a therapeutic state. Potentisation is important because the repeated process of dilution and succussion brings about an energetic change giving the substance powerful curative properties (Kent 2003).

The starting point for any remedy according to a pharmacopoeial monographs which provides a method of preparation, the expression 'mother' denotes that this tincture will give birth to a family of potencies (Owen *et al.* 2007). A homoeopathic mother tincture is a drug solution (alcoholic, hydroalcoholic, aqueous or glyceric) prepared in accordance with homoeopathic pharmacopoeial standards from the corresponding original succuss or other soluble base constituent of the medicine. In these pharmacopoeias, the manufacturing of homeopathic mother tinctures is defined following specific manufacturing procedures, which differ from the manufacturing of phytotherapeutic tinctures. Clinically a herbalist prescribes on the use of the herbs whilst a Homoeopathic mother tincture is prescribed on the basis of the patient's symptoms and signs in accordance with the Law of Similars (Kent 2003).

2.12.8.1 *Arsenicum album*

Patient demonstrates agitation (tendency to move from one place to another) great anxiety, and prostration. This remedy is useful in diabetic neuropathy where there is odour and/or numbness in limbs. It is also good in treating diabetes with boils (Vermeulen and Bakker 1997).

2.12.8.2 *Lycopodium clavatum*

This remedy is useful in diabetes mellitus where a patient shows anger during the disease and loss of self-confidence with an intense desire for sweets. The symptoms are often right sided. This remedy improves liver and kidney function. The diabetic patient suffers from neuropathy, constipation due to inactivity of the rectum, Impotence (Kent 1992).

2.12.8.3 *Phosphoricum acidum*

This remedy is useful in diabetes mellitus of nervous origin such as in cases due to grief, worry and anxiety with an unquenchable thirst. The diabetic patient feels indifferent and apathetic and has poor mental and physical energy. The urine appears milky and contains sugar, deposits of phosphates in urine, or larger quantities of pale colorless urine. Occasionally there may be boils on the body.(Vermeulen and Bakker 1997).

2.12.8.4 *Lacticum acidum*

This remedy is useful in gastro hepatic symptoms of diabetes mellitus such as profuse urine, light yellow glucose containing urine, thirst, nausea, debility, voracious appetite, constipation, dry skin, dry tongue and gastralgia (Kent 1992).

2.12.8.5 *China officinalis*

This remedy is useful when the diabetic patient suffers from weakness and fatigue that results from the loss of fluids such bleeding. The diabetic suffers from expulsion of

gases that does not produce any improvement, loss of vision, ringing in the ears and canine hunger. The diabetic neuropathy is extremely sensitive to touch (Boericke 2001).

2.12.8.6 Silicea terra

This remedy acts on acute and chronic infections in people with diabetes. The skin and bones are prone to suppurative infections. The diabetic patient comes across as shy, insecure and has a fearful of sharp objects (Kent 1992).

2.12.8.7 Sulphur

This remedy acts on almost at all levels, it is useful in diabetics with fluid retention. edema and circulatory problems (Vermeulen and Bakker 1997).

2.12.8.8 Calcarea carbonica

This remedy is useful in obese diabetic patients who have a low thyroid function, that appear “spongy” and have an intolerance for the cold. The diabetic patient may come across as depressed and may have a bad temper (Boericke 2001).

2.12.8.9 Nitricum acidum

This remedy is useful is useful in skin cracks, fissures and ulcers that result from arterial insufficiency. The diabetic patient comes across as nervous, irritable. The urine has strong smell like horse urine. Candilomas and warts may appear in diabetic patients (Vermeulen and Bakker 1997).

2.12.8.10 *Ignatia*

The diabetic patient exhibits marked signs of sadness associated with profound sighs and hysteria, silent penitence and wants to be left alone. The diabetic patient has weakness in the mouth of the stomach with an empty feeling in the stomach. This remedy is useful in neuropathy that acts on the spinal marrow and affects both motor nerve as sensitive. Hysteria (Murphy 2003).

2.12.8.11 *Lachesis*

This remedy is useful in diabetic patients with circulatory problems such as diabetic gangrene, menopause and haemorrhages such as upper digestive tube (bowel) haemorrhages. Retinal haemorrhages (Boericke 2001).

2.12.8.12 *Natrum sulphuricum*

This remedy is useful in diabetic neuropathy that affects the autonomic nervous system. The diarrhoea is aggravated in the morning when the diabetic patient begins to move and is associated with borborygmos on the right side of the abdomen in the ileocecal region. The diabetic patient suffers with a productive cough that is aggravated during the wet time (Phatak 2002).

2.12.8.13 *Argentum metallicum*

This remedy is useful in patients with frequent micturation where the urine is profuse, turbid with a sweet odour. Diabetics usually have problems in the cartilage and joints (Vermeulen and Bakker 1997).

2.12.8.14 *Bryonia alba*

The remedy is indicated in diabetes associated with dry lips and extreme thirst (the first symptom of diabetes). There is a persistent bitter taste. The patient comes across

as languid, morose and dispirited and loses strength through the inability to eat (Murphy 2003).

2.12.8.15 *Thuja*

This remedy is useful in diabetic patients with polyneuritis associated with great pain, polyps, warts and psychosis that have special illusions such as believing that their body and limbs are glass and thinks they have a live animal inside abdomen (Phatak 2002).

2.12.8.16 *Plumbum*

This is one of the most important remedies in diabetes mellitus, it is indicated in diabetic patients who suffers from excessive emaciation, obstinate constipation, greater hunger, sweetish taste in mouth, sweetish belching and vomiting (Phatak 2002).

2.12.8.17 *Uranium niriticum*

This remedy is useful in diabetes mellitus that originates from dyspepsia or indigestion, polyuria, dryness of mouth and skin. The remedy lessens sugar and the quantity of urine. The diabetic patient usually suffers from indigestion and assimilation along with an enormous appetite but loses weight. (Murphy 2003).

2.12.8.18 *Helonias*

The urine contains phosphates and sugar. This remedy is useful in diabetes mellitus associated with melancholia, emaciation, thirst and restlessness (Boericke 2001).

2.13 SYZYGIUM JAMBOLANUM

2.13.1 Introduction

The genus *Syzygium* belongs to the *Myrtaceae* family. *Syzygium jambolanum* is a well-known species also commonly known as Java plum, jambolan, black plum, jamun, Indian blackberry, Portuguese plum, Malabar plum, purple plum, Jamaica and Damson. *Syzygium jambolanum* can also be expressed as *Syzygium cumini*, *Eugenia jambolanum* or *Myrtus cumini* (Ayyanar and Subash-Babu 2012).



Figure 2: *Syzygium jambolanum*
(*Syzygium cumini* 2012)

2.13.2 General description

Syzygium jambolanum originates from the Indian sub-continent, although today *Syzygium jambolanum* can also be found growing throughout the Asian subcontinent, Eastern Africa, South America, Madagascar and has also naturalised to the warmer regions of the United States of America (Baliga *et al.* 2011).

Syzygium jambolanum is an ever-green tree growing up to 50 feet. The fruit of *Syzygium jambolanum* is called Jamun, black plum, Indian blackberry, jambu and jambool. The leaves are elliptic to broadly oblong, smooth, glossy, leathery and fibrous in nature. The bark may appear pale brown when young whilst the mature are slightly dark brown, scaly. The flowers are small and sessile, white in color, fragrant and with thin membranous petals (Shivashankara *et al.* 2013).

Baliga *et al.* (2011) describe two different types of *Syzygium jambolanum* which are based on the description and organoleptic features – the *Kaatha jamun* which are small and acidic to taste, and the *Ras jaman*, that are oblong, dark-purple or bluish, with pink, sweet fleshy pulp and small seeds. The *Syzygium jambolanum* fruits are round, oblong ½ or 2 inches long, the fully ripe fruit are sweet with a mildly sour astringent flavor (Shivashankara *et al.* 2013).

2.13.3 History and folk use

Syzygium jambolanum has a long history in medicinal use in various traditional and folk systems of medicine. All parts of the *Syzygium jambolanum* and the seeds have medicinal value, the fruits are tonic astringent carminative and useful in spleen diseases. The seeds are astringent, diuretic and stop urinary discharges. The bark of the plant is astringent, sweet, carminative, antibacterial, constipating, anti-helmintic and stomachic. The leaves have been widely used to treat diabetes, constipation, leucorrhoea, gastropathy, stranguary and to inhibit blood discharges from the faeces (Shivashankara *et al.* 2013).

In Ayurveda *Syzygium jambolanum* is good for treating pharyngitis, bronchitis, asthma, dysentery and diabetes mellitus. In the Siddha system of medicine *Syzygium jambolanum* is hematinic, and can promote semen production and reduce excessive heat of the body. In the Unani system of medicine *Syzygium jambolanum* acts as a liver tonic, enriches blood, strengthens teeth and gums, and forms a good lotion for removing ringworm infection of the head. The homoeopathic system of medicine uses *Syzygium jambolanum* in the treatment of diabetes mellitus (Shivashankara *et al.* 2013).

Syzygium jambolanum as a homoeopathic remedy is capable of diminishing the amount of sugar in the urine, especially when used in the tincture and lower triturations (Munta 2008). It is a most useful remedy in diabetes mellitus, no other remedy causes a marked degree diminution and disappearance of sugar in the urine (Vermeulen and Bakker 2000).

2.13.4 Phytochemistry

The *Syzygium jambolanum* plant contains many diverse phytochemicals which have numerous health benefits. The pulp of *Syzygium jambolanum* contains anthocyanins, delphinidin, petunidin and malvidin-diglucosides. These compounds are responsible for the bright purple colour of the pulp and have also been shown to stimulate insulin secretion from experimental diabetic rat's pancreatic beta cells *in vitro*. The widely studied seeds of the plant contain jambosine, gallic acid, ellagic acid corilagin, 3,6-hexahydroxy diphenoglucose, 4,6-hexahydroxydiphenoglucose, 1-galloyglucose, 3-galloyglucose, quercetin and β -sorbitol. The stem and the flowers also contain numerous phytochemicals (Shivashankara *et al.* 2013).

2.13.5 Anti-diabetic effects

Syzygium jambolanum has been investigated for its anti-diabetic effects for 127 years. Many experiments on rodents have concluded that the seed, fruit and the bark of *Syzygium jambolanum* have anti-diabetic effects (Shivashankara *et al.* 2013).

Schoenfelder *et al.* (2010) aimed to screen the hypoglycaemic and hypolipidaemic effect of *Syzygium jambolanum* on alloxan-induced and hyperglycaemic normal rats. Rats were divided into three groups; group one received the vehicle (control group), group two received the ethanolic crude extract of leaves from *Syzygium jambolanum* and group three received glibenclimide, an oral hypoglycaemic agent. The acute treatment with *Syzygium jambolanum* caused a significant decrease in blood glucose in hyperglycaemic rats and in glucose, triglycerides and cholesterol in diabetic rats. This study concluded that *Syzygium jambolanum* leaves are a good candidate in the use of alternative and complementary medicine in the management of diabetes mellitus, since they showed hypoglycaemic and hypolipidaemic activity (Schoenfelder *et al.* 2010).

Ayyanar and Subash-babu (2012) compiled a review which was based on the published literature on the antidiabetic effect of *Syzygium jambolanum* in clinical and experimental studies and concluded that *Syzygium jambolanum* caused hypoglycaemic effects on experimental animals. Most of these studies used the crude preparation of the plant. Numerous studies proved *Syzygium jambolanum* acts like sulphonylurea and biguanids to stimulate existing beta cells of Langerhans to secrete insulin and increase glucose use by the liver.

There are very few studies on the effects of *Syzygium jambolanum* on humans. However, Kholi and Singh (1993) conducted a study on 30 patients for 3 months, administering 12 g of *Syzygium jambolanum* seed powder twice daily, a moderate hypoglycaemic effect and ameliorated symptoms associated with diabetes mellitus such as polyuria, polyphagia, weakness and weight loss was observed.

Recently a randomised controlled study was performed on 30 newly diagnosed type 2 diabetes mellitus patients for 6 months. Fifteen were on *Syzygium jambolanum*, five

received Metformin® and 10 diet restrictions and exercise therapy. It was observed that *Syzygium jambolanum* caused a significant decrease in fasting blood sugar, insulin resistance and in high-density lipoprotein at the end of the third month when compared to the baseline. However, there was no reduction in the post-prandial blood sugar and glycosylated haemoglobin at the end of the third and sixth month. It was concluded that *Syzygium jambolanum* has a beneficial effect in the treatment of type 2 diabetes mellitus as it improves the glycaemic profile in newly diagnosed type 2 diabetics (Sahana *et al.* 2010).

2.13.6 Mechanism of action

There are various anti-diabetic mechanism of actions of *Syzygium jambolanum* (Shivashankara *et al.* 2013) These mechanisms of action include:

1. Stimulation of pancreatic action and increase of C-peptide which is an indicator of beta cell function in diabetic rats (Gohil *et al.* 2010) (Achrekar *et al.* 1991; Ravi, Rajasekaran and Subramanian 2005).
2. Restoration of beta cell architecture is reported in experimental diabetic rats of numerous studies (Gohil *et al.* 2010; Achrekar *et al.* 1991).
3. Reduction of oxidative stress which is the primary cause of diabetic complications and antioxidant action (Shivashankara *et al.* 2013).
4. Improvement of glucose utilisation and maintenance of glucose homeostasis by increasing glycogen content in liver and muscle cells, increasing the activities of enzymes crucial for glycogenesis and glycolysis and decreasing enzymes involved in gluconeogenesis (Gohil *et al.* 2010; Achrekar *et al.* 1991; Sharma, Balomajumder and Roy 2008).
5. Prevention of the formation of AGEs that are responsible for diabetic microvascular and macrovascular complications. Chronic hyperglycaemia leads to non-enzymatic glycosylation of proteins which results in the formation of AGEs (Yan, Ramasamy and Schmidt 2008). Glycosylated proteins such as glycosylated haemoglobin, glycosylated albumin and fructosamine are used to indicate the glycaemic control in diabetics. Sharma, Balomajumder and Roy (2008) demonstrated that administering *Syzygium jambolanum* reduced the level of glycosylated haemoglobin in experimental diabetic animals; however similar observations were unseen in human experiments.

6. Reduction in the effects of dyslipidemia in diabetes mellitus. Free radicals target lipoproteins especially low density lipoproteins to cause their oxidation. Oxidised LDL is involved in the pathogenesis of atherosclerosis and vascular complications in diabetes mellitus (Vikrant 2001). The *Syzygium jambolanum* fruit and plant decreases LDL cholesterol, triglycerides and total cholesterol whilst increasing HDL cholesterol in diabetic rats or rabbits (Sharma 1996); Vikrant 2001. Helmstädter (2008) observed beneficial effects in amelioration of dyslipemia in humans although Sahana *et al.* (2010) disagreed.
7. Inhibition of alpha-glycosides which inhibits the digestion of carbohydrates to establish greater glycaemic control in diabetes mellitus (Shivashankara *et al.* 2013).

2.13.7 Toxicology

Yele and Veeranjanyulu (2010) evaluated the acute oral and repeated dose toxicity on a group of albino mice and wistar rats. In the acute toxicity tests, mice received oral doses of *Syzygium jambolanum* 300, 2000, and 5000 mg/kg body weight. Mortality, signs of toxicity, body weight, food consumption, and gross findings were observed for 14 days post-treatment. In repeated dose toxicity, rats received an oral dose of 300, 1000, and 2000 mg/kg body weight, and animals were observed till the 28th day of treatment. Yele and Veeranjanyulu (2010) concluded that *Syzygium jambolanum* can be used continuously and safely because there was no difference in the control and treated group of albino mice and wistar rats. There was no mortality, signs of toxicity, body and organ weights changes reported and concluded that there is little to no toxicity of the substance (Yele and Veeranjanyulu 2010).

Since *Syzygium jambolanum* is reported to have antioxidant and anti-inflammatory properties, Abdalla *et al.* (2011) evaluated the protective effect of *Syzygium jambolanum* seed extract against the poisonous pollutant methylmercury which induces oxidative stress and many ailments. Two day old rats received one oral dose of Methylmercury and two oral doses of *Syzygium jambolanum*. Two days after the intervention, the cerebral cortex, hippocampus, kidney, and liver and urine samples were evaluated and it was concluded that the administration of *Syzygium jambolanum* reverted the toxic effects of methylmercury.

2.14 OTHER COMPLEMENTARY THERAPIES

Ayurveda is a comprehensive holistic system of medicine that has been widely practiced in India for more than 5000 years. The term Ayurveda is a Sanskrit term meaning “science of life”. Ayu means “life” or “daily living” and Ved means “knowing” (Lad 1990)

According to Ayurveda the human body is composed of Mahabhutas, which are basic elements that have properties of space (Akasha), air (Vayu), fire (Tejas), water (Jala) and earth (Prithivi). These basic elements combine to form three psychophysiological principles or Doshas known as Vata, Pitta and Kapha. Vata consists of the lighter elements that have the properties of space and air. Pitta consists of the properties of fire and water and Kapha consists of the heavier elements of water and earth. These Doshas regulate the various functions of the body. Vata regulates functions associated with movement and communication such as blood flow, nerve conduction and intestinal motility. Pitta regulates functions associated with metabolism, digestion and transformation. Kapha regulates function, structure and cohesion (Lad 1990).

Each person has a certain ratio of Vata, Pitta and Kapha that is unique to the individual. This ratio is known as the Prakriti or the psychophysiological constitution. Optimal health and disease is dependent on how these various constituents of the body function together. Optimal health is the result of a state of equilibrium in their functioning and the disturbance of this equilibrium leads to disease. Ayurvedic treatment attempts to establish a balance between the bodily humors, Vata, Pitta and Kapha. There are two types of Ayurvedic treatment – elimination of toxins and the neutralisation of toxins. These treatments may be applied at both the physical and emotional levels (Heyn 1987).

In Ayurveda, type 2 diabetes mellitus is a disease which occurs when toxins get accumulated in the tissue and result in circulation blockage and dosha imbalance. Poor nutrition, poor digestion, imbalance of the nervous system, disturbance of the natural biological cycle, physical and mental stress causes the imbalance of dosha in Ayurveda (Dabur Research Foundation and Dabur Ayurveda Limited 2002).

Ayurveda aims to restore the balance of Dosha in the treatment of diabetes mellitus. In a case where Doshas are slightly increased, restriction of the diet and increased activity is recommend and sufficient. In a case where Doshas are moderately increased, an ayurvedic remedy is recommended along with dietary restrictions and increased activity. In a case where Doshas are markedly increased, Panchakarma, the five actions of detoxification are recommended (Lad 1990).

CHAPTER 3: METHODOLOGY

3.1 TRIAL DESIGN

This clinical randomised double-blind parallel trial was performed following the approval by the ethics committee of the Durban University of Technology (Appendix F). The study took place at the Durban University of Technology's (DUT) Homoeopathic Day Clinic and the Kenneth Gardens Homoeopathic Clinic. Permission was granted by the Clinic Director for the use of the facilities over the clinical trial period. It was conducted for a period of 14 weeks which included a 2 week baseline period followed by a 12 week treatment period, per participant.

The study was double blind, therefore neither the researcher, nor the participants knew which participant belonged to which group; participants were allocated to two different groups by means of equal randomisation. Participants were enrolled by the researcher, and the homoeopathic laboratory technician assigned participants to interventions according to a randomisation list that was drawn up by the research director prior to the study.

In this study the "control" was implemented by recruiting participants that were currently taking Metformin[®] (Glucophage[®]) daily as part of their allopathic management of diabetes mellitus. The inclusion criteria was that even though the participant was taking Metformin[®] daily, as prescribed by their respective physicians, their fasting blood glucose levels were ≥ 7 mmol/L. In other words each participant served as their "active control" due to the fact, that despite being on a daily prescribed dose of Metformin[®] their blood glucose levels were ≥ 7 mmol/L. Creating a control group of participants who were on metformin only would have been superfluous as the effects of Metformin on blood glucose levels are widely documented and would have not had any comparative value in this study. More significant is the individual participants' response before and after the intervention whilst on their individual dose of metformin. This was implemented as opposed to placebo in the ethical interest of

the participants as this may have been medically unsafe due to the nature of the condition.

Further to discontinue their medication abruptly in order to participate in this clinical trial would have posed medical risks to the participants.

Participants were informed of the remedy constituents and made an informed voluntary decision to participate in the trial.

Further this trial seeks to substantiate the use of the homoeopathic substance as an adjunctive therapy for the management of diabetes mellitus in the presence of Metformin[®] (Glucophage[®]) where the fasting blood glucose is ≥ 7 mmol/L.

At the conclusion of the study, thirteen of the original cohort of participants receiving the homoeopathic potency 6CH treatment had completed the full study and eleven of the original cohort who received the homoeopathic mother tincture.

The researcher and the participants were blinded: the researcher wrote out the prescriptions (either the homoeopathic potency 6CH or the mother tincture) and a clinician dispensed the treatments with both the treatments being dispensed in brown 25 ml amber glass bottles in a liquid form to ensure a similar appearance. The researcher explained to each participant how to take the medicine, in order to ensure correct use of the medication.

3.2 SAMPLING METHOD

On receiving approval from the Institutional Research Ethics Committee (IREC), participants were obtained by means of advertising (Appendix G) and the distribution of pamphlets on the Steve Biko, Ritson and ML Sultan campuses of the Durban University of Technology, various health shops and at the Kenneth Gardens homoeopathic clinic. The researcher recruited participants according to the selection criteria listed below (3.3.1).

Potential participants responded to the advertisement by means of a phone call to the researcher. The researcher then scheduled a meeting where a case history (Appendix D) and physical examination (Appendix D) was done at the DUT Homoeopathic clinic or the Kenneth Gardens Homoeopathic clinic in order to determine if they indeed qualified for the study. If participants qualified for the study, participants were required to do a fasting glucose test daily for two weeks using a glucometer that was provided and fill in a log sheet (Appendix C 1) for two weeks which would be utilised as baseline data.

Participants who had an average fasting blood glucose level (baseline after 2 weeks) > 7.0 mmol/L were considered eligible to take part in the study. Participants were required not to make any specific changes to their diet or lifestyle.

All candidates not included in the research study were referred to the DUT homoeopathic clinic or the Kenneth Gardens Homoeopathic Clinic.

3.3 SELECTION CRITERIA

3.3.1 Inclusion criteria

- Participants have to be between 18 and 65 years of age.
- Participants who have been previously diagnosed with type 2 diabetes mellitus and are currently taking only Metformin® (Glucophage®) for the treatment of diabetes.
- Participants who have a stable fasting glucose of ≥ 7.0 mmol/ L.
- Participants who are willing not to change their lifestyle or dietary habits for the duration of the trial.
- Participants need to be fluent and be literate in English or Zulu.

3.3.2 Exclusion criteria

- Persons who are pregnant or lactating.
- Persons diagnosed with glucose-6-phosphate deficiency.
- Persons on chronic medication other than Metformin® (Glucophage®).
- Persons who are illiterate as they are required to read, understand and complete the consent form.

3.4 PARTICIPANTS

Initially the study aimed to be conducted on 30 participants, but the researcher was only able to get 27 eligible participants. Three participants dropped out from the study due to various logistical problems, and other problems such as availability, time constraints, patient compliance etc. Participants were also allowed to withdraw from the study without giving a reason to the researcher. The study was conducted on 24 participants.

A large number of participants (20 participants) resided at the Kenneth Gardens in Umbilo. Kenneth Gardens is the largest municipal housing estate in the city; it provides subsidised housing to approximately 1500-1800 individuals over an estimated 286 units in 28 blocks. People of Kenneth gardens have a wide range of social problems such as alcohol and drug abuse, domestic violence, unemployment and limited access to education. In addition, a large portion of the residents have at least one member of their family with a serious physical or mental illness. The other participants resided in the larger Durban area in Kwa-Zulu Natal in South Africa (Department of Housing 2014).

The first 27 participants (screened against the inclusion and exclusion criteria and displaying an average fasting blood glucose level > 7 mmol/L) were asked to sign an informed consent form (Appendix B) in order to continue with the rest of the study. The participants were then randomly assigned to two groups. Of the 27 participants selected, 24 managed to complete the study.

3.5 STUDY PROCEDURE

First consultation

- At the commencement of the first consultation, each participant received two documents from the researcher: A subject information letter (Appendix A) for their personal perusal and an informed consent form (Appendix B) to sign and return to the researcher.

- A detailed and comprehensive homoeopathic case history (Appendix D) was taken and a physical examination (Appendix E) was performed on each patient by the researcher.
- Patients received a glucometer for the duration of the study in order to allow them to take a blood glucose test daily and fill in a log sheet (Appendix C1) for a period of 2 weeks (baseline).

Second consultation

- The second consultation took place after 2 weeks (day 14) in order to establish a baseline for the patient. The baseline is the average level of the participant's blood glucose before experimental intervention. It is utilised as a reference point. This baseline value was recorded in the log sheet (Appendix C1).
- If the participant's average fasting blood glucose level (baseline after 2 weeks) was > 7.0 mmol/L then the participant was considered eligible to take part in the study.
- Blood was drawn by a qualified nurse at the Isolempilo Clinic at the Durban University of Technology or the Kenneth Gardens Homoeopathic Clinic for glycosylated haemoglobin (HbA1C) to be measured at the Global Clinical and Viral Laboratory using the Beckman method. This reading would form a baseline for HbA1C. A qualified nurse tied a tourniquet on the person's upper arm, to locate a vein in the inner elbow region, a needle was inserted into the vein, the vacuum action draws the blood through the needle into an attached tube, and collection of the sample took only a few minutes. This test required 5 ml of blood.
- An appointed homoeopathic practitioner dispensed medication to the respective groups according to the randomisation sheet drawn up by the research director in the department of Homoeopathy at the Durban University of Technology.

On each of the third and fourth consultations a follow-up case history was taken. An appointed homoeopathic physician dispensed medication to the respective groups according to the randomisation sheet drawn up by the research director in the Department of Homoeopathy at the Durban University of Technology.

At the fifth follow-up consultation, which was the final consultation, blood was drawn by a Qualified Nurse at the Isolempilo Clinic at the Durban University of Technology or the Kenneth Gardens Homoeopathic Clinic for glycosylated haemoglobin (HbA1C) to be measured at the Global Clinical and Viral Laboratory using the Beckman method.

The experimental medication was dispensed in liquid format (50 ml) and comprised either of *Syzygium jambolanum* 6CH or the *Syzygium jambolanum* homoeopathic mother tincture in an amber glass bottle.

Participants were asked to return for a follow-up consultation every 4 weeks and were called telephonically every week to ensure participant compliance for a period of 3 months

Participants self-administered a fasting blood glucose test daily and filled in a log sheet (Appendix C 2) for a period of 14 weeks that included a 2 week baseline period followed by a 12 week treatment period.

3.6 TREATMENT

The *Syzygium jambolanum* homoeopathic potency 6CH and the *Syzygium jambolanum* homoeopathic mother tincture were used as interventions in this study.

3.6.1 Experimental medicines

The *Syzygium jambolanum* 6CH utilised for the study was prepared at the Durban University of Technology Homoeopathic Day Clinic dispensary. The *Syzygium jambolanum* homoeopathic mother tincture was obtained from Fusion Homoeopathics (retailer). The medicines were in a liquid format and were dispensed in 50 ml amber glass bottles from the second follow-up consultation up to the fourth follow-up consultation.

3.6.1.1 Manufacture of *Syzygium jambolanum* 6CH

Syzygium jambolanum 6CH was prepared at the homoeopathic laboratory at the Durban University of Technology. Preparation was based on homoeopathic principles and a qualified homoeopathic laboratory technician supervised the researcher during the preparation.

Syzygium jambolanum 6CH was produced according to the German Pharmacopeia Method 5a, using the *Syzygium jambolanum* mother tincture as a starting material (Appendix H). The *Syzygium jambolanum* 6CH was dispensed in a 30% alcohol base.

Each participant had five consultations with the researcher at monthly intervals, one initial plus four follow up consultations. During each consultation the participant's subjective and objective responses to the treatment were assessed and recorded as per homoeopathic case history.

3.6.1.2 Manufacture of *Syzygium jambolanum* homoeopathic mother tincture

Syzygium jambolanum mother tincture was obtained from Fusion Homoeopathics, a homoeopathic pharmaceutical company based in Johannesburg, and dispensed in a 30% alcohol base.

Syzygium jambolanum mother tincture was prepared according to the German Homoeopathic Pharmacopoeia method 4A, using the dried fruit as a starting material. Certificate of Analysis for the specific batch was provided to the researcher by Fusion Homoeopathics (Appendix J).

3.7 INTERVENTION

Each participant was given 50 ml of either the homoeopathic potency 6CH or the homoeopathic mother tincture at the second, third and fourth follow-up consultation. Participants were instructed to take 30 drops of their medication in a quarter glass of water 30 minutes after a meal twice daily. It was assumed that all participants administered the medicines as directed.

3.8 OUTCOME MEASURES

During the study participants monitored their fasting blood glucose and complete a log sheet.

Participants were required to have blood drawn during the first and fifth consultation for the glycosylated haemoglobin (HbA1C) test.

3.8.1 Fasting blood glucose

Fasting blood glucose was measured daily by the participants using a glucometer (Bayer Ascensia Elite) which was provided to each participant for the duration of the study.

Participants were shown how to use the glucometer correctly during the first consultation and also received instructions on how to perform a blood glucose test (Appendix I).

Participants were required to record their blood glucose levels on a log sheet (Appendix C) on their own every morning before breakfast.

There were two log sheets provided during the study, the first log sheet (C 1) had to be completed after the first consultation for two weeks before intervention to establish the baseline. The second log sheet (C 2) had to be completed for 12 weeks after the start of the intervention.

3.8.2 Glycosylated haemoglobin (HbA1C)

The glycosylated haemoglobin test was administered before intervention and after intervention. The glycosylated haemoglobin test before intervention was the baseline.

A qualified nurse drew blood from the participants during the second and fifth follow up consultations. The blood was fetched by the Global and Viral Laboratory personnel for analysis.

3.9 RELIABILITY AND VALIDITY MEASURES

All participants were asked not to make any substantial changes to their lifestyle especially their diet and exercise program for the duration of the study (14 weeks study that included a 2 week baseline period followed by a 12 week treatment period).

All medication was manufactured according the German Pharmacopeia. *Syzygium jambolanum* mother tincture was obtained from a licensed manufacturer, which employs good manufacturing practice and standard operating procedures. A certificate of analysis was provided was to the researcher.

At no time were the researcher and supervisor cognizant of whether participants were receiving the mother tincture or the homoeopathic potency 6CH. All medication was dispensed in an amber glass bottle ensuring that medicines had a similar appearance.

Blood was drawn by a qualified nurse. All blood samples were tested at the Global and Viral laboratory Services in Durban. The Beckman assay was used.

3.10 DATA COLLECTION AND DATA ANALYSIS

Only data collected from the log sheets (Appendix C) and the laboratory results (glycosylated haemoglobin levels) were used for analysis.

Statistical analysis was conducted using MS-EXCEL® as well as SPSS® software suite. Descriptive and inferential statistical techniques were used. The descriptive procedures used were various tables and graphs as well as summary statistics including but not limited to means, proportions and percentages. Inferential statistics included hypotheses testing techniques. All tests set the type 1 error at 5% (0.05).

A p value of less than 0.05 resulted in a significant result in which case the Null Hypothesis was rejected.

3.11 ETHICAL CONSIDERATIONS

Participation was purely voluntary and participants were allowed to withdraw from the study at any time without explanation. The researcher respected confidentiality of the participants by replacing names with numbers traceable only by the researcher and supervisor therefore ensuring anonymity. All participants' information was kept in a locked room and no identity information was used in research

CHAPTER 4: RESULTS

4.1 INTRODUCTION

The aim of this research study was to determine the efficacy of *Syzygium jambolanum* 6CH and *Syzygium jambolanum* homoeopathic mother tincture on daily fasting blood glucose and glycosylated haemoglobin levels in type 2 diabetes mellitus patients on Metformin®.

The sample group consisted of 24 participants between the ages of 18-65 years. Participants had to have been diagnosed with type 2 diabetes mellitus prior to the study, and had to meet the inclusion and exclusion criteria before being selected. All participants were required to remain on Metformin®.

This three month two week trial was a double-blind study in which participants were divided into two groups. The one group received the homoeopathic potency, the other received the homoeopathic mother tincture. All participants were advised to administer 30 drops of the medication supplied, twice daily. It was recommended that participants have a 30 minute interval after meals before taking their medication.

Participants were required to have their HbA1c levels tested. This test was conducted twice during the course of the trial. The first test was conducted prior to administration of the remedy and the second test was conducted once the three month trial period had passed. In addition to the HbA1c blood test, participants had to test their fasting blood glucose levels once daily using a blood-glucose finger prick test before breakfast.

Participants were made aware of any discomfort they might experience during phlebotomy. Precautions were taken to ensure that this was minimal. The results of this study were made available to participants on request. The researcher had follow-up consultations with participants on a monthly basis.

Results statistically analysed were obtained from the participants fasting blood glucose readings documented on the log sheet (Appendix C1 and C2) and the laboratory results for the HbA1c blood tests.

4.2 STUDY COMPLIANCE

Initially the study was aimed to be conducted on 30 participants, but the researcher was only able to recruit 27 eligible participants. Three dropped out from the study due to various logistical problems such as availability and patient compliance. Participants were also allowed to withdraw from the study without giving reasons to the researcher. The study was conducted on 24 participants.

At the completion of the study, 13 of the original cohort of participants who had received the homoeopathic potency 6CH treatment completed the full study and 11 of the original cohort who received the mother tincture.

There were no adverse effects reported or anticipated, therefore risk factors for participants were minimal. All questions and concerns were answered and addressed by the researcher.

4.3 DEMOGRAPHICS

4.3.1 Gender

There were 24 participants in the study, consisting of 4 (17%) males and 20 (83%) females. See Figure 3.

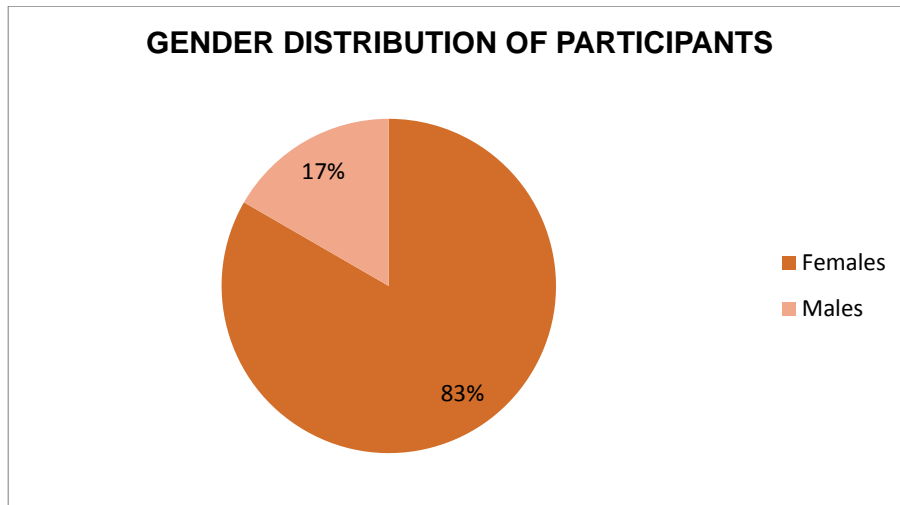


Figure 3: Gender distribution of participants (%)

4.3.2 Age

The study was open to participants between 18 and 65 years of age, but participants were between the ages of 30-65 years of age. Of the 24 participants there was 1 participant (4%) between the ages of 30-39 years, 1 participant (4%) between the ages of 40-49 years, 8 participants (34%) between the ages of 50-59 years and 14 participants (58%) between the ages of 60-65 years. See Figure 4.

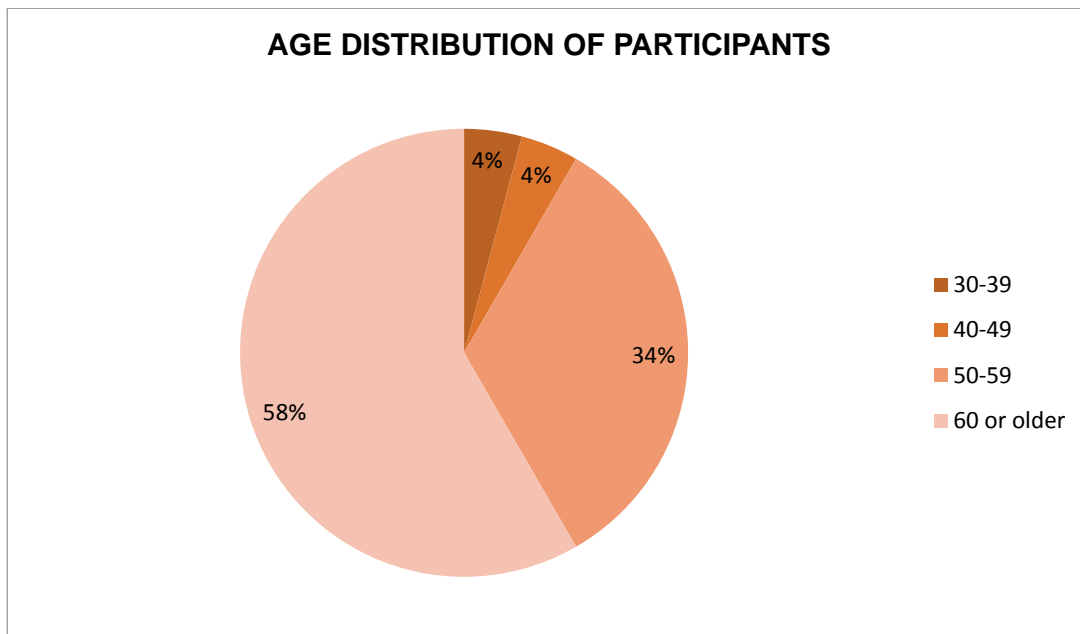


Figure 4: Age distribution of participants (%)

4.3.3 Race

Of the 24 participants, 8 (33%) were black, 9 (39%) were Indian, 6 (25%) were white and 1 (4%) was coloured. See Figure 5.

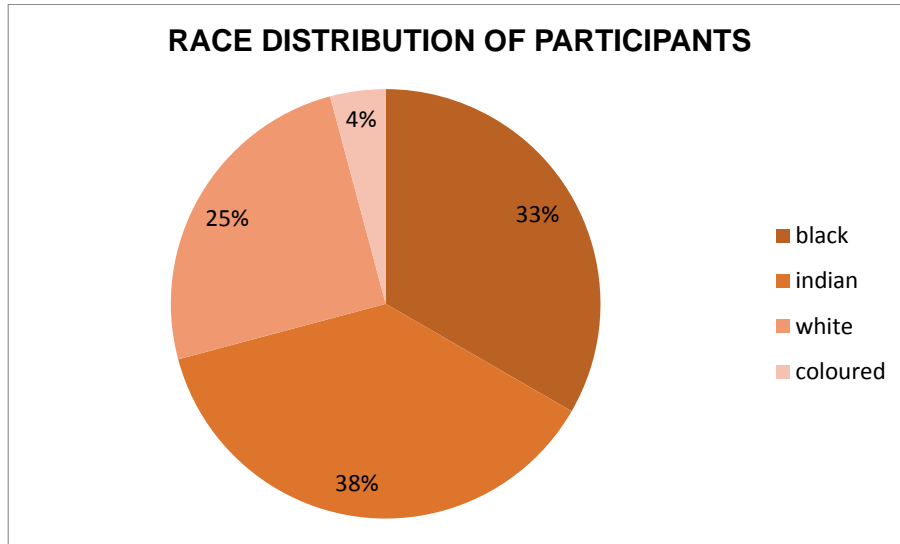


Figure 5: Race distribution of participants (%)

4.3.4 Intervention

Of the 24 participants, 13 (54%) received *Syzyguim jambolanum* 6CH and 11 (46%) received *Syzyguim jambolanum* homoeopathic mother tincture. See Figure 6.

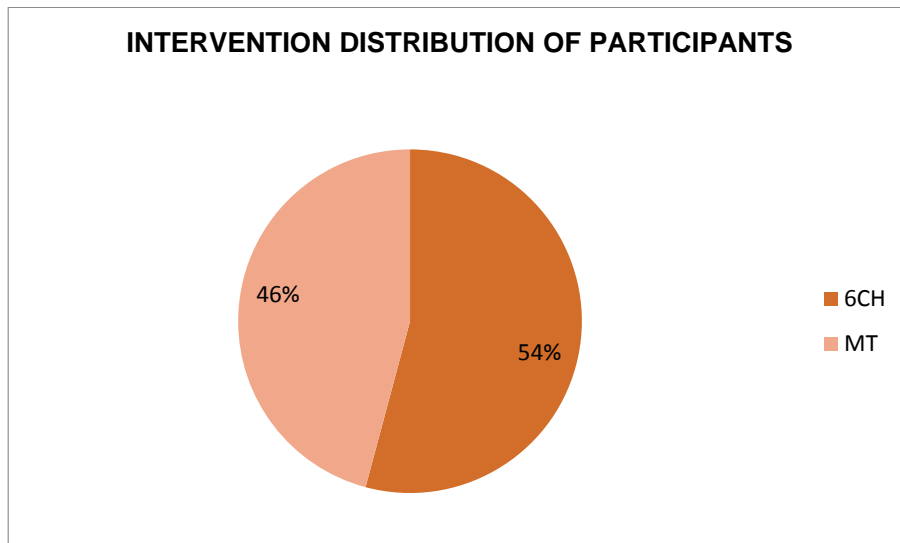


Figure 6: Intervention distribution of participants (%)

4.4 STATISTICAL ANALYSIS

The statistical analysis of these results needed to elucidate the following: the presence or absence and statistical significance of any improvement within groups (i.e. the group treated with *Syzygium jambolanum* 6CH and the group treated with *Syzygium jambolanum* mother tincture) as measured by either the mean daily fasting blood glucose scores over time and/or the glycosylated haemoglobin levels.

The presence or absence and statistical significance of any difference in results between the groups (i.e. the group treated with *Syzygium jambolanum* 6CH and the group treated with *Syzygium jambolanum* mother tincture) as measured by either the mean daily fasting blood glucose scores over time and/or the glycosylated haemoglobin levels.

4.3.1 Intra-group analysis

This section comprises the analysis of each group in terms of pre- and post-intervention blood results (both fasting glucose and HbA1C). The intra-group analysis was performed using the repeated measures ANOVA. This tests for significant changes in the means of the measurements within each group. The null hypothesis is tested at the level of 5% significance i.e. the possibility of the observed data being the result of chance is less than 5% ($p = 0.05$).

Null hypothesis (H_0): The observed change in fasting blood glucose levels/glycosylated haemoglobin (HbA1C) is not due to the treatment effect.

Alternative Hypothesis (H_1): The observed change in fasting blood glucose levels/glycosylated haemoglobin (HbA1C) is due to the treatment effect.

Each of the treatment groups were analysed separately using the repeated measures ANOVA test for the fasting blood glucose data, and the 2-related samples (t-test) for the glycosylated haemoglobin.

Tables 1-10 summarise the results of the intra-group analysis of each of the two treatment groups

To analyse the fasting blood glucose data, individual data points were aggregated into weekly means. This allowed interpretability and accuracy of interpretation of the results of the ANOVA.

4.3.1.1 Intra-group analysis of group treated with *Syzygium jambolanum* 6CH (fasting blood glucose)

Table 1: Means of each of the weeks of blood glucose measurements for the *Syzygium jambolanum* 6CH treated group

Blood Glucose Mean	Mean	Std. Deviation
Wk1	11.8802	4.89315
Wk2	11.6451	4.50209
PostWk1	10.3000	5.09656
PostWk2	9.8286	4.65232
PostWk3	10.2209	5.22517
PostWk4	9.8264	4.89115
PostWk5	9.7077	5.30009
PostWk6	9.3659	5.15387
PostWk7	9.0890	4.97222
PostWk8	9.1923	4.65645
PostWk9	9.3747	4.35871
PostWk10	8.9901	4.17587
PostWk11	8.9319	3.83865
PostWk12	8.5637	3.51811
PostWk13	8.6590	3.51701

Table 1 demonstrates a clear and consistent reduction in the mean blood glucose levels over the course of the treatment. This is graphically illustrated in Figure 7.

Table 2: Results of the repeated measures ANOVA of the fasting blood glucose data for the *Syzygium jambolanum* 6CH treated group

Blood Glucose		F Score	Sig.
Correction	Huynh-Feldt	7.171	.000

As is reflected in Table 2 above a statistically significant score of $p < 0.05$ is documented so one can conclude that the observed reduction in fasting blood glucose levels is not due to random variation, but due to the treatment effect.

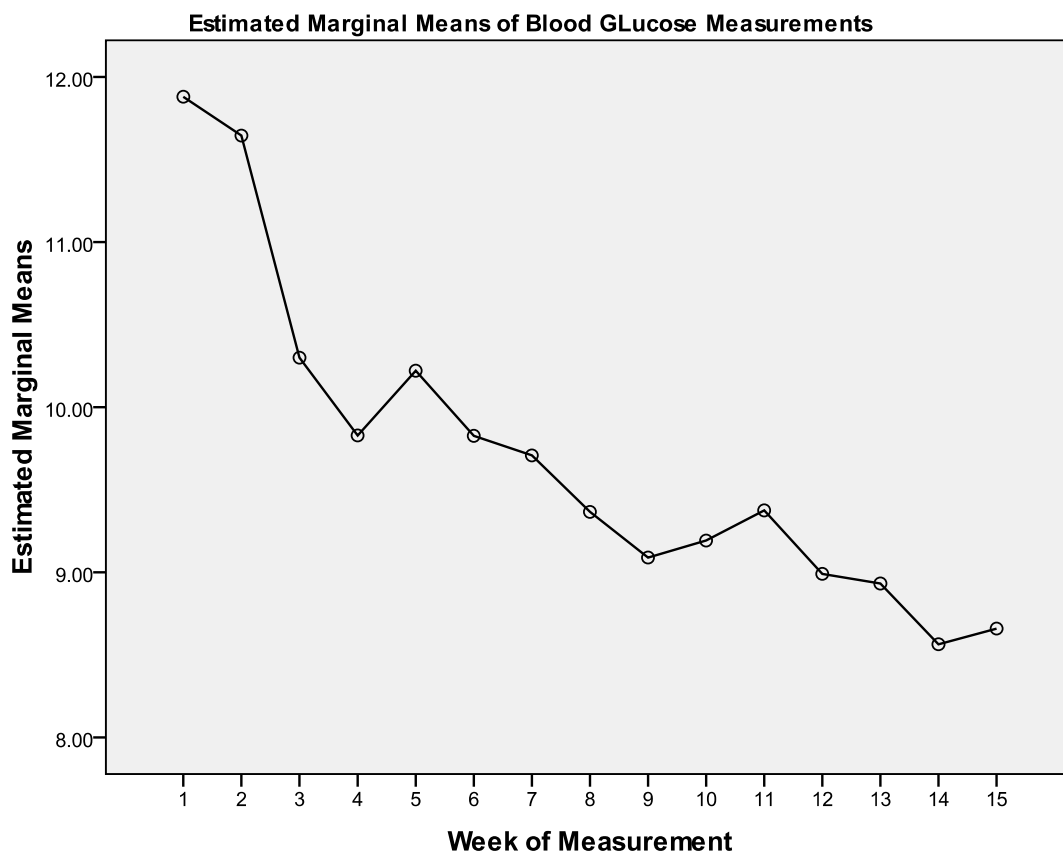


Figure 7: Weekly means of repeated blood glucose measurements for the *Syzygium jambolanum* 6CH treated group

As documented in Table 1 it is evident that there is a significant reduction in the mean weekly blood glucose measurements over the course of the trial. i.e. week 1 the mean blood glucose level was 11.8802 with a standard deviation of 4.89315 whereas in week 13 the mean blood glucose was 8.6590 with a standard deviation of 3.51701.

Of particular interest for purposes of the study is to assess the significance of the first two weekly means (pre-intervention measurements) against each other and against the first few weeks of the treatment. This follows from the graphical view above in which the reduction in mean blood glucose level appeared most marked from week 2 where the mean glucose value was 11.6451 with a mean glucose deviation of 4.50209 to week 4 where the mean glucose value was 9.8264 with a mean deviation of 9.7077 (i.e. in the immediate time subsequent to commencing treatment with *Syzygium jambolanum* 6CH).

This was analysed as part of the General Linear Model of SPSS analysis function. The results of this analysis are shown in Table 3.

Table 3: Comparison between weekly mean blood glucose readings. Significance level was 95 % i.e. 0.05

Means compared	Mean difference	Significance level	Significant
Week 1 vs Week 2	0.235	0.271	No
Week 1 vs Week 3	1.580	0.000	Yes
Week 1 vs Week 4	2.052	0.006	Yes
Week 2 vs Week 3	1.345	0.005	Yes
Week 2 vs Week 4	1.816	0.022	Yes
Week 2 vs Week 5	1.424	0.002	Yes

As documented in Table 3 it is evident that there is a significant reduction in the mean weekly blood glucose levels. This reduction was most marked from week 2 to week 4. The mean glucose value compared between week 2 and 4 was 1.816 with a significance value that is less than 0.005.

This effect is also investigated in the next section in which the glycosylated haemoglobin levels (which reflect long term blood glucose levels) from before and after the treatment are compared.

4.3.1.2 Intra-group analysis of group treated with *Syzygium jambolanum* 6CH (glycosylated haemoglobin)

The HbA1C test is an accurate reflection of the glucose control over the preceding two to three months. This test indicates what percentage of haemoglobin proteins are 'glycosylated'.

Table 4: Descriptive statistics for glycosylated Haemoglobin data for *Syzygium jambolanum* 6CH treated group

HbA1C	Mean	Std. Deviation	Minimum	Maximum
HbA1CBefore	9.9231	2.69325	7.80	15.80
HbA1CAfter	9.0231	2.86681	6.80	15.60

As documented in Table 4 t there is evident reduction in the mean value of the HbA1C levels post treatment. ie The mean value of HbA1C before treatment was 9.9231 with the standard deviation of 2.69325 and the mean value of the HbA1C levels post treatment is 9.0231 with a standard deviation of 2.86681.

Table 5: Results of the 2 related sample test (t-test) for glycosylated Haemoglobin data for *Syzygium jambolanum* 6CH treated group

T-TEST	HbA1CAfter - HbA1CBefore
Z	-3.194a
Asymp. Sig. (2-tailed)	.001

As reflected from Table 5 above a statistically significant score of $p < 0.005$ is documented, it is apparent that there is a statistically significant reduction in the HbA1C result following treatment with *Syzygium jambolanum* 6CH. The reduction in HbA1C is further illustrated in Figure 8.

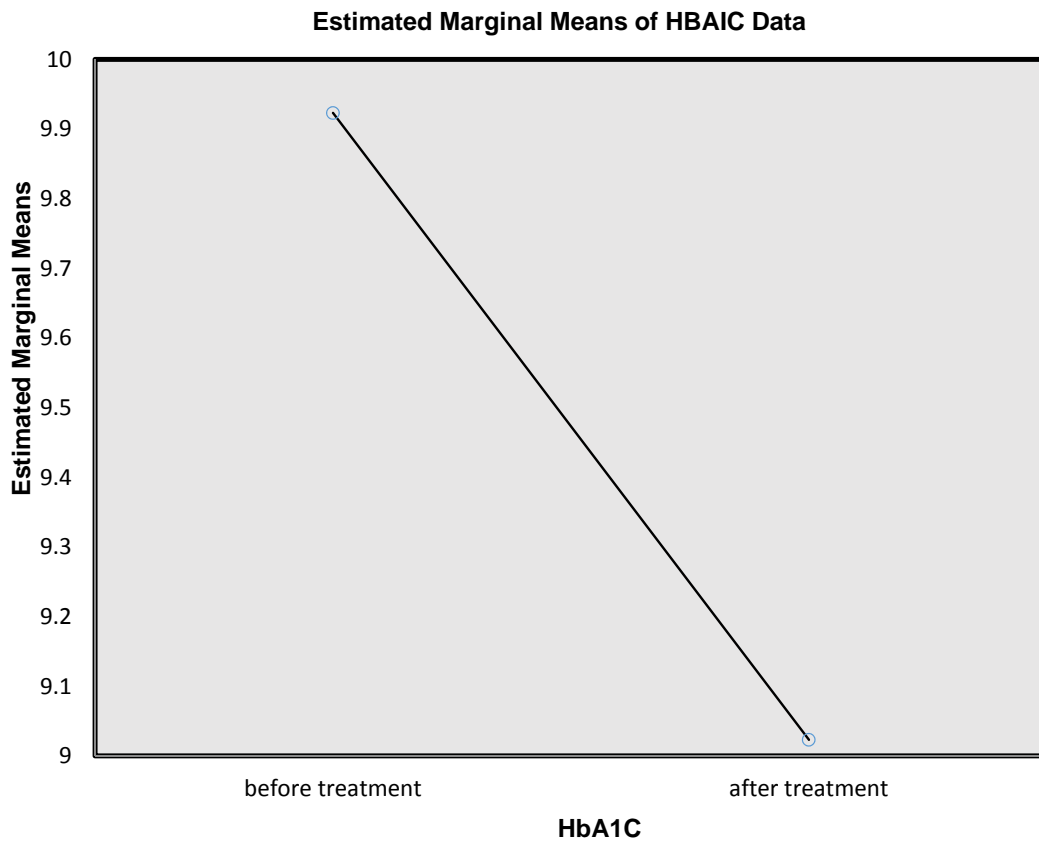


Figure 8: Reduction in mean HbA1C levels in the group treated with *Syzygium jambolanum* 6CH

While the reduction is statistically significant (i.e. it is unlikely to have occurred as a result of random variation within the sample) the treatment effect is moderate to small. This contrasts with the observed changes in weekly mean blood glucose readings which were larger. This may be explained by the duration of the trial; 90 days of post

treatment may not have been sufficient time for the previous glycosylation level to completely change to reflect the lowering blood glucose levels. In this case the HbA1C levels lag the blood glucose levels.

4.3.1.3 Intra-group analysis of the group treated with *Syzygium jambolanum* Homoeopathic mother tincture (fasting blood glucose)

Table 6: Means of each of the weeks of blood glucose measurements for the *Syzygium jambolanum* mother tincture treated group

Blood Glucose Mean	Mean	Std. Deviation
Wk1	9.0338	.90701
Wk2	9.0779	.58820
PostWk1	8.2779	.51474
PostWk2	7.7130	.78785
PostWk3	7.6182	.98101
PostWk4	7.7299	1.08657
PostWk5	7.7753	.68530
PostWk6	7.6104	.75076
PostWk7	7.5494	1.02616
PostWk8	6.9494	.88639
PostWk9	7.0377	.60522
PostWk10	6.8351	.93955
PostWk11	7.0351	.61140
PostWk12	6.8701	.99958
PostWk13	6.8591	.70496

Table 6 demonstrates a clear and consistent reduction in the mean blood glucose levels over the course of the treatment. This is graphically illustrated in Figure 9. As

Table 7: Repeated measures ANOVA of the fasting blood glucose data for the *Syzygium jambolanum* mother tincture treated group

Blood Glucose		F Score	Sig.
Correction	Huynh-Feldt	12.121	.000

As reflected in Table 7 above a statistically significant score of ($p < 0.05$) is documented so one can conclude that the observed reduction in fasting blood glucose levels is not due to random variation, but due to the treatment effect. The reduction in fasting glucose levels is graphically illustrated in Figure 9.

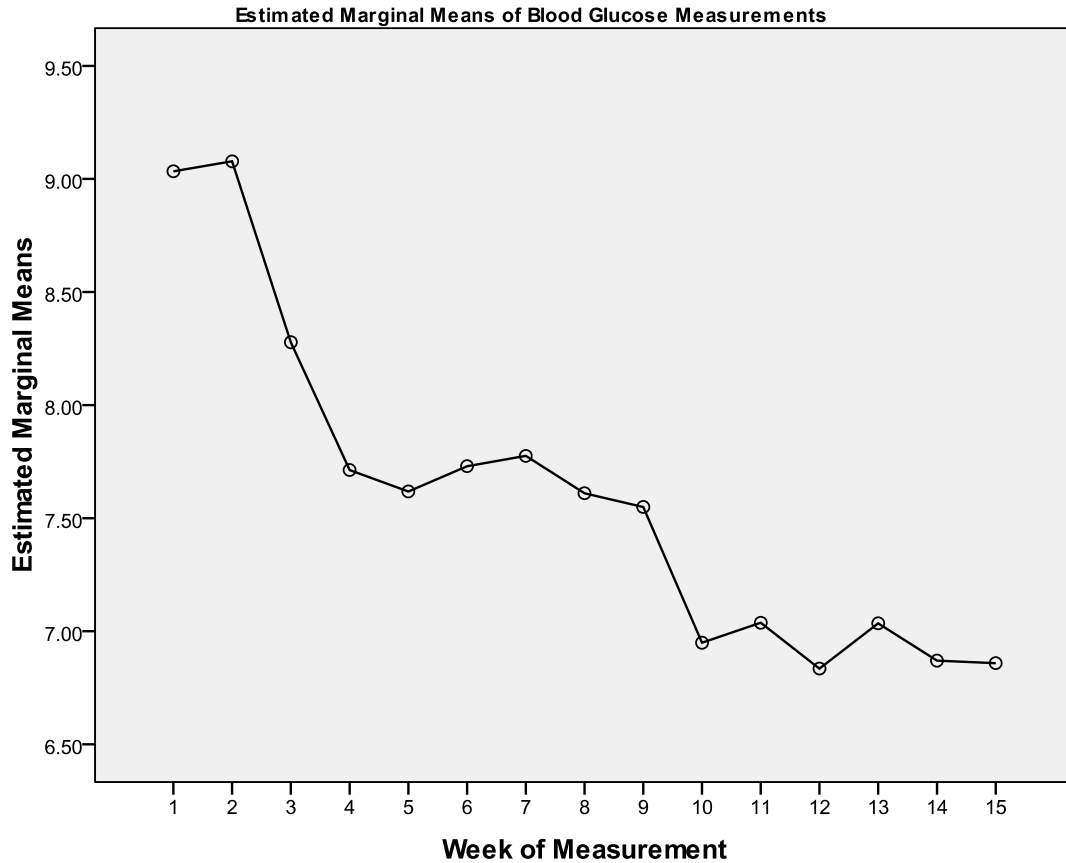


Figure 9: Weekly means of repeated blood glucose measurements for the *Syzygium jambolanum* mother tincture treated group

As documented in Table 6 it is evident that there is a significant reduction in the mean weekly blood glucose measurements over the course of the trial. i.e. week 1 the mean blood glucose level was 9.0338 with a standard deviation of 0.90701 whereas in week 13 the mean blood glucose was 6.8591 with a standard deviation of 0.70496.

Of particular interest for purposes of the study is to assess the significance of the first two weekly means (pre-intervention measurements) against each other and against the first few weeks of the treatment. This was analysed as part of the General Linear Model of SPSS analysis function. The results of this analysis are shown in Table 8.

Table 8: Comparison between weekly mean blood glucose readings. Significance level was 95 % i.e. 0.05

Means compared	Mean difference	Significance level	Significant
Week 1 vs Week 2	-0.044	0.800	No
Week 1 vs Week 3	0.756	0.038	Yes
Week 1 vs Week 4	1.321	0.006	Yes
Week 2 vs Week 3	0.800	0.014	Yes
Week 2 vs Week 4	1.365	0.001	Yes
Week 2 vs Week 5	1.460	0.002	Yes

As documented in Table 8 the reduction in mean blood glucose level appeared most marked from week 2 to week 5 (i.e. in the immediate time subsequent to commencing treatment with *Syzygium jambolanum* mother tincture). The mean glucose value compared between week 2 and 5 was 1.460 with a significance value that is less than 0.005.

From Figure 9 and Table 8 it is evident that there is a statistically significant reduction in the mean weekly blood glucose levels. This started only after treatment was commenced.

This effect is investigated in the next section in which the glycosylated haemoglobin levels (which reflect long term blood glucose levels) from before and after the treatment are compared.

4.3.1.4 Intra-group analysis of group treated with *Syzygium jambolanum* mother tincture (glycosylated haemoglobin)

The HbA1C test is an accurate reflection of glucose control over the preceding two to three months. This test indicates what percentage of haemoglobin proteins are 'glycosylated'.

Table 9: Descriptive statistics for glycosylated Haemoglobin data for *Syzygium jambolanum* mother tincture treated group

HbA1C	Mean	Std. Deviation	Minimum	Maximum
HbA1CBefore	8.6091	.53564	8.00	9.90
HbA1CAfter	8.3000	.54589	7.50	9.40

As documented in Table 9 there is evident reduction in the mean value of the HbA1C levels post treatment. ie The mean value of HbA1C before treatment was 8.6091 with the standard deviation of 0.53564 and the mean value of the HbA1C levels post treatment is 8.3000 with a standard deviation of 0.54589.

Table 10: Table 10 Results of the 2 related sample test (t-test) for glycosylated haemoglobin data for *Syzygium jambolanum* mother tincture treated group

T-TEST	HBA1CAfter - HBA1CBefore
Z- score	-2.988
Significance level	.003

As reflected from Table 10 above a statistically significant score of $p < 0.05$ is documented, it is apparent that there is a statistically significant reduction in the HbA1C result following treatment with *Syzygium jambolanum* homoeopathic mother tincture treatment group. The magnitude of this reduction in HbA1C is further illustrated in Figure 10.

Estimated Marginal Means of HBA1C Data

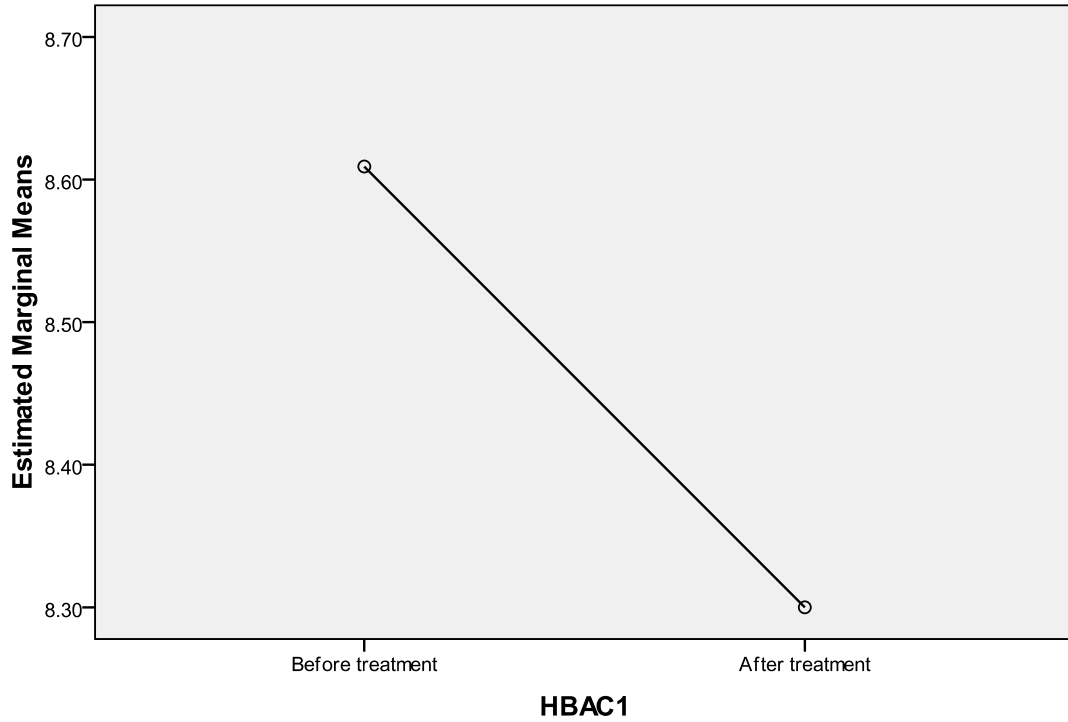


Figure 10: Reduction in mean hBA1C levels in the group treated with *Syzygium jambolanum* mother tincture

While the reduction is statistically significant (i.e. it is unlikely to have occurred as a result of random variation within the sample) the treatment effect is moderate to small. This however may form the topic of future research i.e. is the treatment effect related to length of time on treatment or is it a moderate/small effect which stabilises over a short time period.

4.3.2 Inter-group analysis: fasting blood glucose

4.3.2.1 Inter-group analysis (fasting blood glucose)

The fasting blood glucose measurements were grouped into weekly mean scores to facilitate interpretability and accessibility. These weekly mean scores were analysed using the General Linear modelling function in SPSS 17.0. The group allocation was used as the conditional (independent) variable, and the blood glucose means used as repeated measure dependant variables.

This tested the null hypothesis that there was no significant difference between data measurements from the different treatment groups (i.e. 6CH and mother tincture treated groups). The hypothesis was set at a 5% significance level ($p = 0.05$). The null hypothesis was rejected if the significance of the test score was less than 5% i.e. a less than 5% chance that the observed differences in data were due to chance.

Null hypothesis (H_0): There is no statistically significant difference in the blood glucose measurements between the 6CH group and the mother tincture group.

Alternative hypothesis (H_1): There is a statistically significant difference in the blood glucose measurements between the 6CH group and the mother tincture group.

Table 11: Descriptive statistics for the inter group analysis

	Group_Alloctn	Mean	Std. Deviation	N
Wk1	1.00	11.8802	4.89315	13
	2.00	9.0338	.90701	11
	Total	10.5756	3.86634	24
Wk2	1.00	11.6451	4.50209	13
	2.00	9.0779	.58820	11
	Total	10.4685	3.52600	24
PostWk1	1.00	10.3000	5.09656	13
	2.00	8.2779	.51474	11
	Total	9.3732	3.83752	24
PostWk2	1.00	9.8286	4.65232	13
	2.00	7.7130	.78785	11
	Total	8.8589	3.56678	24
PostWk3	1.00	10.2209	5.22517	13
	2.00	7.6182	.98101	11
	Total	9.0280	4.05192	24
PostWk4	1.00	9.8264	4.89115	13
	2.00	7.7299	1.08657	11
	Total	8.8655	3.75948	24
PostWk5	1.00	9.7077	5.30009	13
	2.00	7.7753	.68530	11
	Total	8.8220	3.97840	24
PostWk6	1.00	9.3659	5.15387	13
	2.00	7.6104	.75076	11
	Total	8.5613	3.86032	24
PostWk7	1.00	9.0890	4.97222	13
	2.00	7.5494	1.02616	11
	Total	8.3833	3.73776	24
PostWk8	1.00	9.1923	4.65645	13
	2.00	6.9494	.88639	11
	Total	8.1643	3.59965	24
PostWk9	1.00	9.3747	4.35871	13
	2.00	7.0377	.60522	11
	Total	8.3036	3.38916	24
PostWk10	1.00	8.9901	4.17587	13
	2.00	6.8351	.93955	11
	Total	8.0024	3.26878	24
PostWk11	1.00	8.9319	3.83865	13
	2.00	7.0351	.61140	11
	Total	8.0625	2.96353	24
PostWk12	1.00	8.5637	3.51811	13
	2.00	6.8701	.99958	11
	Total	7.7875	2.76317	24
PostWk13	1.00	8.6590	3.51701	13
	2.00	6.8591	.70496	11
	Total	7.8340	2.74023	24

Table 11 demonstrated a clear that there was a gradual reduction in mean blood glucose levels as the trial progresses. This is graphically illustrated in Figure 11. On inspection it is also apparent that the mother tincture group has a lower average blood glucose level throughout the trial (both pre- and post-treatment).

Table 12: Table showing F-score for repeat measure ANOVA ordered by treatment group

	F Score	Significance level
Blood Glucose*Group Allocation	0.677	0.623

While both groups had significantly reduced blood glucose levels over the course of the trial, this does not seem to be dependent on which treatment group. This is confirmed by the test statistic (F score) of the repeated measures ANOVA ordered by treatment group. As reflected in Table 12 above, a significant score of 0.623 was documented.

This conclusion is illustrated in Figure 11 and Figure 12 below.

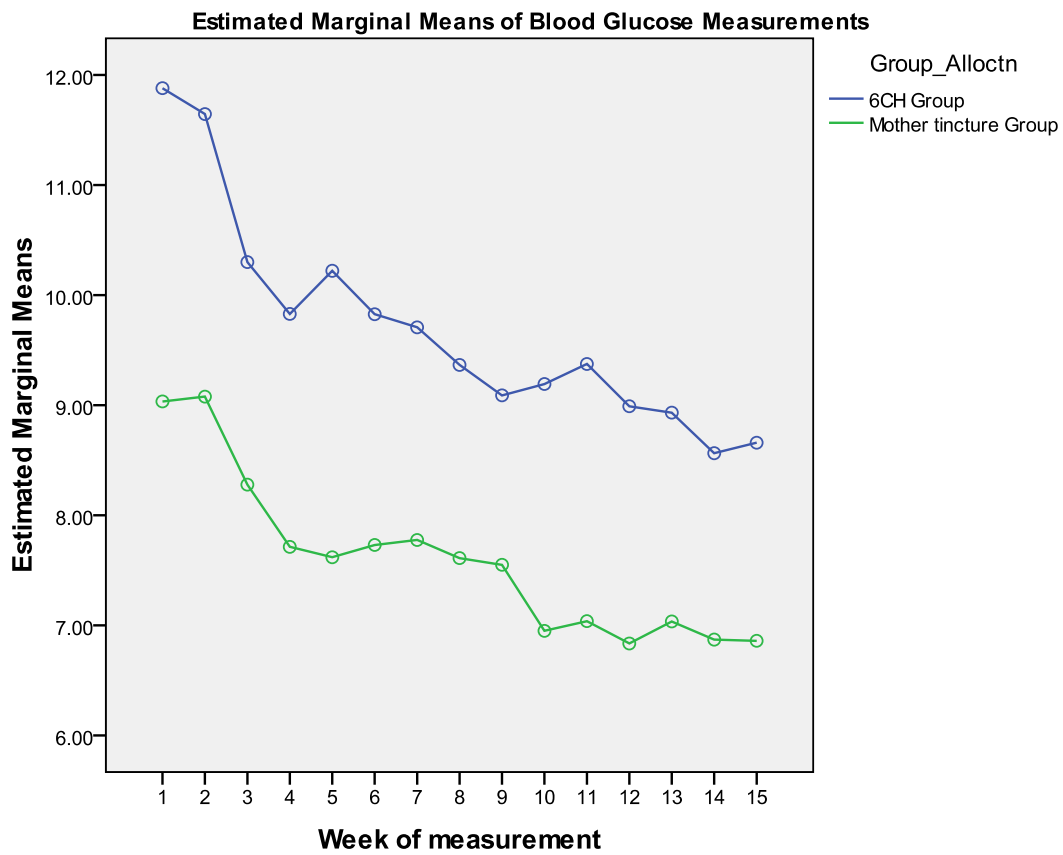


Figure 11: Changes in weekly mean blood glucose level through the trial- ordered by treatment group

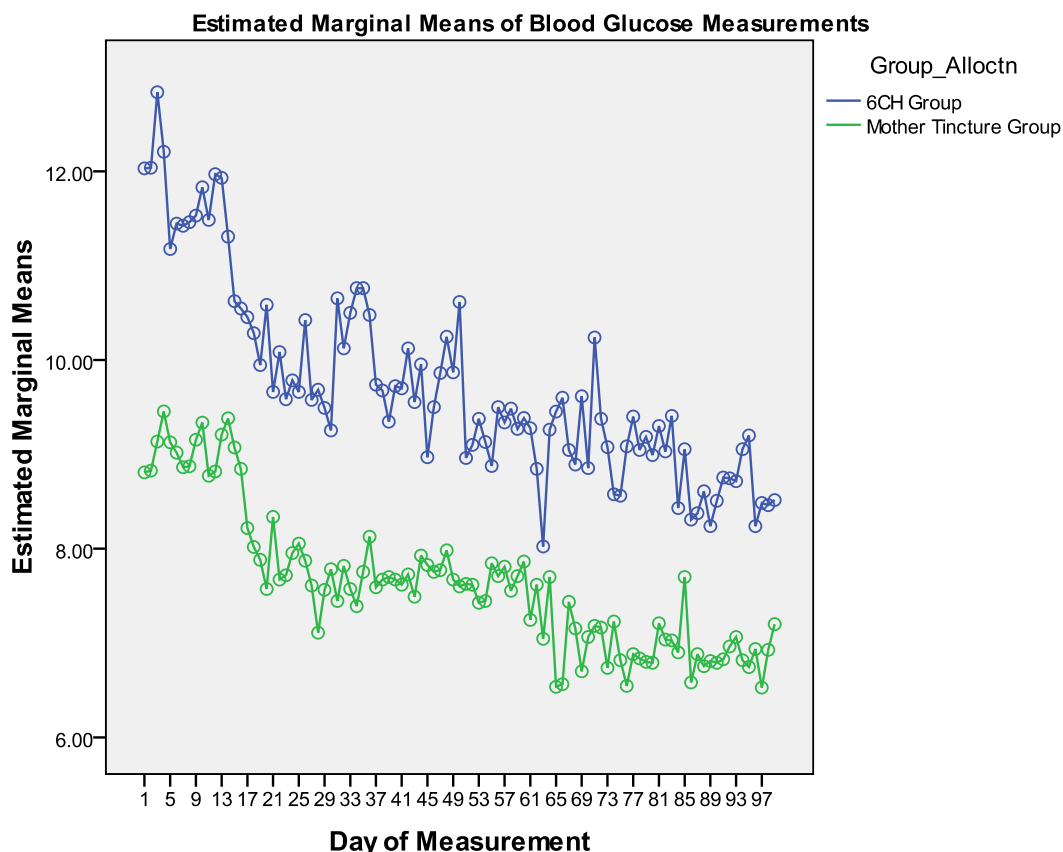


Figure 12: Changes in daily blood glucose level through the trial- ordered by treatment group

From Figure 11 and Figure 12 it can be seen that both treatment groups have a significant reduction in blood glucose levels across the trial period. This reduction was most significant at the commencement of the treatment (whether 6CH or homoeopathic mother tincture). Table 13 below summarises the result of this test to confirm this conclusion.

Table 13: Summary of the Mann-Whitney U test on the Mean blood glucose levels before and after treatment initiation, ordered by group

	AVeBefore	AVeAfter	Significant
Mann-Whitney U	49.000	64.000	
	-1.304	-.435	
Significance (2 tailed)	.192	.664	No

Two new variables were computed from the data. These were the mean blood glucose level before treatment, and the mean blood glucose level after treatment. These variables were analysed using the Mann-Whitney U test to check for any significant

differences between the two treatment groups. The significance level was set at 5%. There was no statistical significant difference between the mean blood glucose level before and after treatment.

Both groups demonstrated significant and marked reductions in blood glucose levels after treatment (see results previously), however there was no statistically significant difference in the extent of this treatment effect depending on treatment group

4.3.2.2 Inter-group analysis: HbA1C levels

4.3.2.2.1 Mann-Whitney Test

The inter-group analysis of the changes in glycosylated haemoglobin was conducted using the Mann-Whitney U test for 2 independent samples. This tested the null hypothesis that there was no significant difference between data measurements from the different treatment groups (i.e. 6CH and mother tincture groups). The hypothesis was tested at a 5% significance level ($p = 0.05$). The null hypothesis was rejected if the significance level of the test score was less than 5% i.e. with a less than 5% chance that an observed difference in the data was due to chance.

Null hypothesis (H_0): There is no difference in the data observations between the 6CH group and the mother tincture group.

Alternative hypothesis (H_1): There is a significant difference in the data observations between the 6CH and the mother tincture group.

Table 14: Summary of the Mann-Whitney U test on glycosylated haemoglobin levels, ordered by group

	HBA1CBefore	HBA1C After	Significant
Mann-Whitney U	54.500	53.000	
Z	-0.990	-1.073	
Significance (2 tailed)	0.322	0.283	No

Both groups demonstrated significant and marked reductions in glycosylated hemoglobin after treatment (see results previously), however there was no statistically

significant difference in the extent of this treatment effect depending on treatment group.

This conclusion is reflected in the Figure 13 which charts HbA1C before and after treatment, by group.

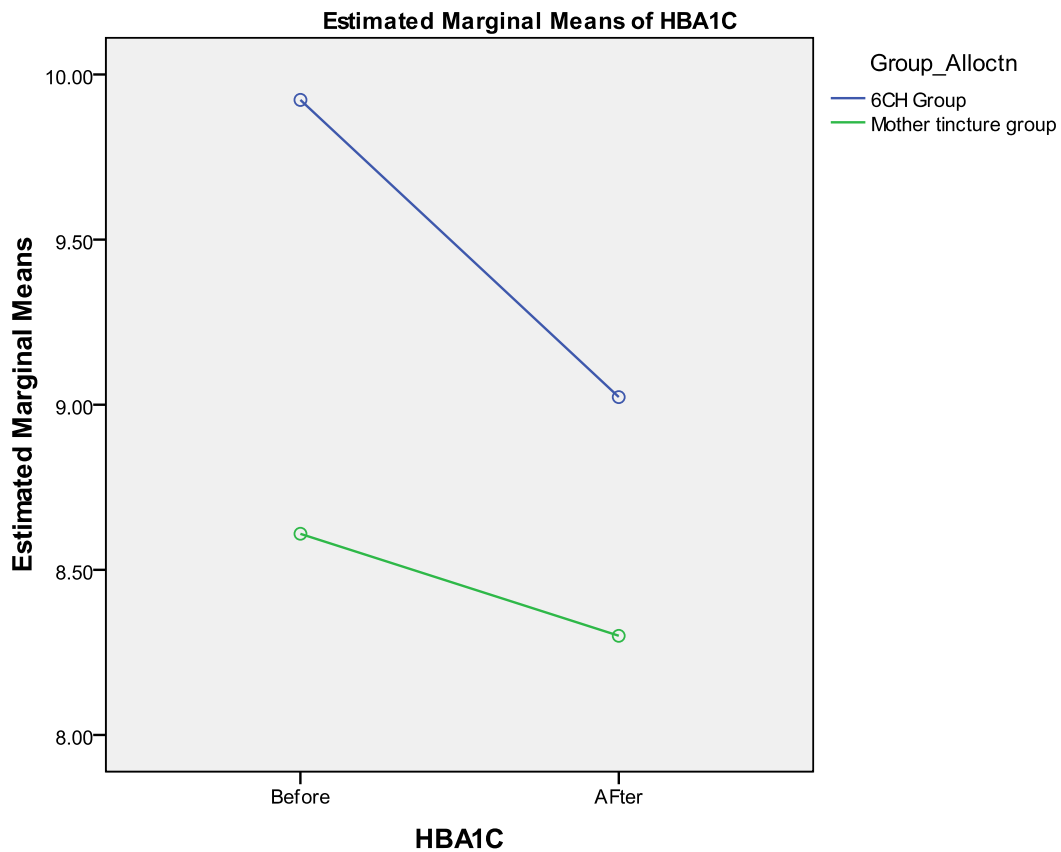


Figure 13: HbA1C before and after treatment ordered by group

In conclusion, both groups demonstrated statistically significant reductions in both fasting blood glucose levels (mean and daily) as well as in the glycosylated haemoglobin levels. There was no statistically significant difference between the two treatment groups before and after treatment.

CHAPTER 5 DISCUSSION

5.1 INTRODUCTION

The aim of this double-blind, randomised clinical trial was to determine the efficacy of *Syzygium jambolanum* 6CH and *Syzygium jambolanum* homoeopathic mother tincture on daily fasting blood glucose and glycosylated haemoglobin levels in type 2 diabetes mellitus patients on Metformin®.

5.2 FASTING BLOOD GLUCOSE

Participants were required to record their fasting blood glucose levels once daily in the mornings before meals using a glucometer.

Participants were required to document their fasting blood glucose readings in a log book for two weeks (Appendix C1) without medication to establish the baseline readings and then document readings for 12 weeks in a log sheet whilst on the treatment (Appendix C2).

Each of the treatment groups (*Syzygium jambolanum* 6CH or *Syzygium jambolanum* mother tincture) were analysed separately using the repeated ANOVA test intra-group analysis for the fasting blood glucose data. The General Linear Model of SPSS analysed the baseline glucose data. The Mann-Whitney U test was used to conduct inter-group analysis of both the treatment groups.

5.3 GLYCOSYLATED HAEMOGLOBIN

Participants were required to have their HbA1c levels tested. This test was conducted twice for the purpose of this trial. The first test was conducted prior to administration of the remedy and the second test was conducted once the three month trial period was completed.

Each intervention was analysed separately (*Syzygium jambolanum* 6CH or *Syzygium jambolanum* mother tincture) using the t-test (2-related samples) for the intra-group analysis for glycosylated haemoglobin data.

The inter-group analysis of the changes in glycosylated haemoglobin was conducted using the Mann-Whitney U test for 2 independent samples. This tested the null hypothesis that there was no significant difference between data measurements from the different treatment groups (i.e. 6CH and mother tincture groups).

5.4 INTERPRETATION OF RESULTS

The first hypothesis hypothesised that *Syzygium jambolanum* 6CH will be effective in reducing the fasting blood glucose and glycosylated haemoglobin levels in type 2 diabetes mellitus patients on Metformin®.

The second hypothesis hypothesised that *Syzygium jambolanum* homoeopathic mother tincture will be effective in reducing the fasting blood glucose and glycosylated haemoglobin levels in type 2 diabetes mellitus patients on Metformin®.

The intra-group analysis analysed the presence or absence and statistical significance of any improvement within groups (i.e. the group treated with *Syzygium jambolanum* 6CH and the group treated with *Syzygium jambolanum* mother tincture) as measured by either the mean daily fasting blood glucose scores over time and/or the glycosylated haemoglobin levels.

The null hypotheses hypothesised that there will be no difference in effect between *Syzygium jambolanum* 6CH and *Syzygium jambolanum* homoeopathic mother tincture in reducing the fasting blood glucose and glycosylated haemoglobin levels in type 2 diabetes mellitus patients on Metformin®. The null hypothesis was tested at the level of 5% significance i.e. the possibility of the observed data being the result of chance is less than 5% ($p = 0.05$).

The inter-group analysis analysed the presence or absence and statistical significance of any difference in results between the groups (i.e. the group treated with *Syzygium*

jambolanum 6CH and the group treated with *Syzygium jambolanum* mother tincture) as measured by either the mean daily fasting blood glucose scores over time and/or the on glycosylated haemoglobin levels.

5.4.1 Interpretation of the intra-group analysis

5.4.1.1 Interpretation of the intra-group analysis of group treated with *Syzygium jambolanum* 6CH (fasting blood glucose)

To analyse the fasting blood glucose data of the *Syzygium jambolanum* 6CH treatment group, individual data points were aggregated into weekly means, to allow for interpretability and accuracy of interpretation (Table 1).

The weekly means of the fasting blood glucose is illustrated in Table 1 which reflects significant reduction in the weekly mean blood glucose. i.e. week 1 the mean blood glucose level was 11.8802 with a standard deviation of 4.89315 whereas in week 13 the mean blood glucose was 8.6590 with a standard deviation of 3.51701.

The repeated ANOVA test was used to assess the statistical significant changes in the means of the measurement of *Syzygium jambolanum* 6CH. The null hypothesis is tested at the level of 5% significance.

The weekly means of the fasting blood glucose is also illustrated in a Table 2 using the repeated ANOVA measures. The p value < 0.001 this reflects statistical significance and it can be concluded that the observed reduction in fasting blood glucose levels is not due to random variation, but due to the treatment.

All participants measured the fasting blood glucose for two weeks before intervention (baseline) to assess the significance of the treatment. Table 3 shows the comparison between the weekly mean blood glucose readings and it can be seen that there is statistically significant reduction in the mean weekly blood glucose levels which commenced after treatment. The mean fasting blood glucose difference in this group

between week 1 and week 2 is 0.235 at baseline and $p=0.271$ showing no statistical significance but the mean fasting blood glucose difference between week 2 and week 5 is 1.424 and $p<0.005$, this reflects a statistical significance.

5.4.1.2 Interpretation of the intra-group analysis of group treated with *Syzygium jambolanum* 6CH (glycosylated haemoglobin)

Table 4 shows the descriptive statistics for the glycosylated haemoglobin data (pre- and post-treatment) and reflects a reduction of the mean value of the glycosylated haemoglobin levels post-treatment. ie The mean value of HbA1C before treatment was 9.9231 with the standard deviation of 2.69325 and the mean value of the HbA1C levels post treatment is 9.0231 with a standard deviation of 2.86681.

The mean value was interpreted using the t-test (2 related sample test), a statistically significant score of $p < 0.005$ is documented $p < 0,005$ in the glycosylated haemoglobin following treatment with *Syzygium jambolanum* 6CH which is further illustrated in Figure 8.

Although there is a statistically significant reduction in the glycosylated haemoglobin, the effect is moderate to small. This contrasts with the observed changes in weekly mean blood glucose readings which were larger. This may be explained by the duration of the trial.

The 90 days of post treatment may not have been sufficient for the previous glycosylation level to completely change to reflect the lowering blood glucose levels. In this case the HbA1C levels fail to maintain the decrease at a similar rate to the blood glucose levels observed.

5.4.1.3 Interpretation of the intra-group analysis of group treated with *Syzygium jambolanum* homoeopathic mother tincture (fasting blood glucose)

To analyse the fasting blood glucose data of the *Syzygium jambolanum* mother tincture group, individual data points were aggregated into weekly means, to allow for interpretability and accuracy of interpretation (Table 6). The repeated ANOVA test was used to assess the significant changes in the means of the measurement of *Syzygium jambolanum* homoeopathic mother tincture. The null hypothesis was tested at the level of 5% significance.

The weekly means of the fasting blood glucose is illustrated in Table 7 using the repeated ANOVA measures and shows a statistically significant reduction in fasting blood glucose levels. A statistically significant score of ($p < 0.05$) is documented therefore the observed reduction in fasting blood glucose levels is not due to random variation, but due to the treatment.

All participants measured the fasting blood glucose for two weeks before intervention (baseline) to assess the significance of the treatment. Table 8 shows the comparison between the weekly mean blood glucose readings and it can be seen that the statistically significant reduction in the mean weekly blood glucose levels commenced only after treatment. The mean fasting blood glucose difference in this group between week 1 and week 2 is -0.044 at baseline and $p=0.800$ showing no statistical significance but the mean fasting blood glucose difference between week 2 and week 5 (commencement of treatment) is 1.460 and $p<0.005$, this reflects a statistical significance.

5.4.1.4 Interpretation intra-group analysis of group treated with *Syzygium jambolanum* homoeopathic mother tincture (glycosylated haemoglobin)

Table 9 shows the descriptive statistics for glycosylated haemoglobin data (pre- and post-treatment) and reflects a reduction in the mean value of the glycosylated haemoglobin levels post-treatment. The mean value of HbA1C before treatment was

8.6091 with the standard deviation of 0.53564 and the mean value of the HbA1C levels post treatment is 8.3000 with a standard deviation of 0.54589.

The mean value interpreted using the t-test (2 related sample test) documented a statistically significant score of $p < 0.05$, it can be concluded that there was reduction in the glycosylated haemoglobin following treatment with *Syzygium jambolanum* 6CH which is further illustrated in Figure 10. A statistically significant score of $p < 0.05$ is documented.

Although there is a statistically significant reduction in the glycosylated haemoglobin, the treatment effect is moderate to small. This contrasts with the observed changes in weekly mean blood glucose readings which were larger. This may be explained by the duration of the trial.– 90 days of post treatment may not have been sufficient for the previous glycosylation level to completely change to reflect the lowering blood glucose levels. In this case the HbA1C levels lag the blood glucose levels.

5.4.2 Interpretation of the inter-group analysis

5.4.2.1 Interpretation of the inter-group analysis of the (fasting blood glucose)

The fasting blood glucose measurements were grouped into weekly mean scores to facilitate interpretability and accessibility (Table 11) and analysed using the General Linear modelling function in SPSS 10.0. The group allocation was used as the conditional (independent) variable, and the blood glucose means used as repeated measure dependent variable.

A gradual reduction is observed in mean blood glucose level as the trial progressed. On inspection it is also apparent that the mother tincture group had a lower average blood glucose level throughout the trial (both pre- and post-treatment). While both groups had a significantly reduced blood glucose levels over the course of the trial, this does not seem to be dependent on which treatment grouping. This was confirmed by the test statistic (F score) of the repeated measures ANOVA (Table 12) with a significant score of 0.623.

The mean blood glucose level before treatment and the mean blood glucose level after treatment illustrated in Table 13 confirmed this conclusion. These variables were analysed using the Mann-Whitney U test to check for any significant differences between the two treatment groups. The significance level was set at 5%. There was no statistical significant difference between the mean blood glucose level before and after treatment.

5.4.2.2 Inter-group analysis of the glycosylated haemoglobin

The inter-group analysis analysed the changes of the glycosylated haemoglobin levels. Using the Mann-Whitney U test which tested for 2 independent samples. This tested the null hypothesis that there was no significant difference between data measurements from the two different treatment groups (i.e. 6CH and mother tincture groups).

The summary of the glycosylated haemoglobin levels is illustrated in Table 14. No statistically significant difference between the glycosylated haemoglobin levels before and after treatment.

Both groups demonstrated significant and marked reductions in blood glucose levels after treatment (see results previously), however there was no statistically significant difference in the extent of this treatment effect depending on treatment group.

This conclusion was further illustrated in Figure 13 which charts HbA1C before and after treatment.

5.5 FINAL OBSERVATIONS

5.5.1 Metformin®

Metformin® is a widely used and prescribed drug in the treatment of type 2 diabetes mellitus but type 2 diabetes mellitus remains a leading cause of cardiovascular disorders, blindness, end-stage renal failure, amputations and hospitalisations because of uncontrolled diabetes mellitus. It is well established in the study that the risk of microvascular and macrovascular complications is related to glycaemia. Glycaemic control remains a major focus of therapy in the treatment of diabetes mellitus (Amod *et al.* 2012).

Participants were only accepted into the study if they were on Metformin® and their glucose levels had to be equal to or higher than the recommended 7mmol/L. This meant that participants were on Metformin® but still experienced hyperglycaemia.

Results in this study established that both *Syzygium jambolanum* homoeopathic mother tincture and *Syzygium jambolanum* 6CH is an effective adjunct to Metformin® in the management of uncontrolled type 2 diabetes mellitus because of the observed reduction of fasting blood glucose levels.

5.5.2 Cost effectiveness

Both the prevalence and incidence of type 2 diabetes mellitus are increasing worldwide, particularly in developing countries. This results in an economic burden because of the associated diabetes complications and treatment in healthcare systems especially in government clinics where there are not enough resources.

The use of *Syzygium jambolanum* mother tincture is common practice in homoeopathy in the treatment of type 2 diabetes mellitus which can be costly. Both the *Syzygium jambolanum* homoeopathic mother tincture and *Syzygium jambolanum* 6CH

effectively reduced fasting blood glucose levels in the study. *Syzygium jambolanum* 6CH can be a cheaper option in community clinics.

5.6 COMPARISON OF STUDIES

To date there are no human homoeopathic research studies conducted to investigate the effect of *Syzygium jambolanum* in homoeopathic potency and mother tincture on the effect of blood glucose levels, many rely on animal research studies.

Jamaludin, Budin, and Katharin (2010) aimed to validate the effects of *Syzygium jambolanum* homoeopathic mother tincture on the glucose levels, lipid profile and histology of pancreas of streptozotocin induced diabetic rats.

Thirty-two male rats of body weight 250-300g were randomly divided into four groups. A week after adaptation, two groups were injected with a single dose (45 mg/kg) of streptozotocin, on the third day the streptozotocin rats were confirmed diabetic with the measurement of blood glucose level higher than 13.8mmol/L. The treatment of the homoeopathic mother tincture *Syzygium jambolanum* was then administered for 28 days.

The four groups were the non-diabetes mellitus rat without treatment, non-diabetes mellitus rats with treatment, diabetes mellitus rats without treatment and the diabetes mellitus rats with treatment.

After four weeks of treatment, the rats were sacrificed and a blood sample and the pancreas was collected for biochemical analysis. Results of the mean plasma glucose level of the treated diabetes group of rats showed a significant reduction (61.71%) as compared to the non-treated diabetes group of rats. The treated diabetes group of rats showed significantly reduced mean level of plasma total cholesterol, triglycerides and low density lipid cholesterol compared to the non-treated diabetes group rats. The mean high density lipid cholesterol level was significantly increased in treated diabetic group rats as compared to the non-diabetic rats. The histology examination showed the presence of denser beta cell distribution and larger islets of Langerhans of treated diabetes group as compared to the non-treated diabetes group rats. Jamaludin , Budin,

and Katharin (2010) concluded that the homoeopathic mother tincture *Syzygium jambolanum* can be used as a treatment for diabetes mellitus because the study proved that it has hypoglycaemic and hypolipidaemic activity (Jamaludin, Budin, and Katharin 2010).

Maiti (2013) aimed to evaluate the ameliorating effects of *Syzygium jambolanum* homoeopathic mother tincture on carbohydrate and lipid metabolic disorders in streptozocin induced diabetic male albino rats.

Twenty four Wistar strain albino rats weighing 140-180g were randomly divided into four groups (control group, diabetic group, diabetic with *Syzygium jambolanum* group and diabetic with glibenclimide group) with six rats in each group. Diabetes mellitus was induced on overnight fasted rats by administering streptozotocin at the dose of 40mg/kg.

Results of the study showed *Syzygium jambolanum* homoeopathic mother tincture decreased fasting blood glucose levels and improved the activity of the carbohydrate metabolic key enzymes. The serum lipid profile biomarkers such as triglycerides, total cholesterol and low density lipoprotein cholesterol were significantly ameliorated in the diabetic rats with *Syzygium jambolanum* homoeopathic mother tincture group as compared the untreated diabetic rat group.

Results of the study also indicated that the treatment of homoeopathic mother tincture *Syzygium jambolanum* in diabetic rats restored body weight and significantly controlled the elevated blood glucose level as compared to the untreated diabetic group. The levels of glycogen in the liver and skeletal muscle tissues were recovered by treatment. Levels of serum urea, uric acid, creatinine and free radicals that were increased in diabetic rats subsided after the treatment with *Syzygium jambolanum*.

Maiti (2013) concluded that the homoeopathic mother tincture of *Syzygium jambolanum* has therapeutic effect on metabolic disorders and oxidative injuries in Streptozotocin induced diabetic male albino rats (Maiti 2013).

This study had a similar approach to a study conducted by Govender (2011) where he compared *Mormodica charantia* homoeopathic mother tincture and *Mormodica charantia* 6CH. The same measurement tools were used, and there was no control group. Both treatment groups reflected a statistically non-significant difference between the two groups when comparing reduction in fasting blood glucose levels. Group 1 (*Momordica charantia* homoeopathic mother tincture) reflected a non-significant reduction in glycosylated haemoglobin levels while Group 2 (*Momordica charantia* 6CH) reflected a statistically significant increase over time in HbA1C levels. There were no significant differences between the two groups when comparing reduction in HbA1C levels.

5.7 LIMITATIONS OF THE STUDY

Several difficulties were experienced during the planning and execution of this study. These include feasibility, cost, time constraints and ethical considerations. Although the study was originally designed to include 30 participants, the researcher had to request for a reduction in numbers towards the end of the study, due to patient compliance. The final study included 24 participants. 27 participants were recruited in the study and three did not complete the study. 11 participants received the homoeopathic mother tincture while 13 the homoeopathic potency.

There was an interval of four weeks between the second, third, fourth and fifth consultation, ideally this should have been a period of two weeks which would have allowed for closer monitoring of patients, ensuring better patient compliance and correct recording of daily fasting blood glucose levels.

Although participants were provided with clear instructions with respect to recording of fasting blood glucose, administration of medication and requested not to make changes to their lifestyle, diet and, quantity of exercise it was not possible to verify objectively whether each patient complied accordingly. This relates specifically to the measuring and recording of daily fasting blood glucose levels. In this study participants were each provided with a glucometer and were required to measure their blood glucose levels every morning before breakfast. The procedure entailed pricking the fingertip with a lancet and placing the required amount of blood onto a test strip which

was inserted into the glucometer for analysis followed by correct recording of the reading on the log sheet. Although the correct procedure was clearly demonstrated at the first consultation process as with any self-administered diagnostic test a margin for error does exist such as inadequate lancing and applying too little blood, it is also possible that participants may have forgotten to perform the test on occasion or performed the test after eating. It is possible that such errors in data collection may have contributed to the paradoxical relationship between mean fasting blood glucose levels and mean HbA1C levels noted in the study.

The implications of small sample size on factors such as statistical power, external validity, sampling error and likelihood of biased data may influence results. A larger sample is thus an ideal in this particular study. The extent of the disease in patients may potentially negatively influence the study by producing statistical outliers and skewed data. A larger sample may have resulted in more normally distributed data. Although a large sample is theoretically ideal the feasibility of such a study is questionable due to budgetary and time limitations and challenges to patient compliance and commitment.

To date no human homoeopathic study on *Syzygium jambolanum* has been done therefore it is difficult to explain the complete action of the remedy.

The degree and extent of diabetes in each patient varied depending on the factors such as length of disease, control of disease, use of Metformin®, age, lifestyle etc. Amod *et al.* (2012) recommend that HbA1C levels under 7% are desirable. Patients that participated in this trial had HbA1C levels ranging from 5.3% to 12.4% therefore it can be inferred that some patients were at a more advanced stage of the disease and thus may have responded better had this not been the case. Ideally this variable should have been controlled either by stratified sampling or by limiting the extent or degree of existing disease in the inclusion/exclusion criteria. This variable particularly in light of the small sample size skewed the data due to the presence of statistical outliers.

Dr. Hahnemann believed that the body contains an inborn power called the vital force which is an energy responsible for healthy running of the body and coordinating its defenses against disease. If the vital force is disturbed by stress, poor diet, lack of

exercise, environmental changes illness results. Symptoms of illness are the outward manifestation of the vital force trying to maintain balance and restoring order (Hahnemann 1996). Type 2 diabetes mellitus is a chronic disease with advanced derangements of the vital force of the patient. To accommodate each patient's stage of disease in a chronic state, a deeper understanding of the entire disease process is required. A comprehensive homoeopathic case taking process will reveal the deeper malady of the patient and thus a deeper acting remedy i.e. the patient's simillimum can be selected. Such a method would consider the patients individual stage of disease as well as the sensitivity of the patient due to the disease stage. The sensitivity of the patient varies according to the patients' health, their reaction to external stimuli, the stage of disease and use of allopathic medication, drugs and supplementation.

CHAPTER 6 CONCLUSION AND RECOMMENDATIONS

6.1 CONCLUSION

The aim of this study was to determine the efficacy of *Syzygium jambolanum* 6CH and *Syzygium jambolanum* homoeopathic mother tincture by reducing the daily fasting blood glucose and glycosylated haemoglobin levels in type 2 diabetes mellitus patients on Metformin® so that it is as close to the recommended normal ranges as possible thus reducing the risk of both chronic microvascular and macrovascular diabetic complications and explore alternative methods of treatment of this condition.

Results from the intra-group analysis showed an improvement of the fasting blood glucose and glycosylated haemoglobin levels in both groups. Thus, both the homoeopathic potency and homoeopathic mother tincture of *Syzygium jambolanum* directly caused a significant reduction of the fasting blood glucose and glycosylated haemoglobin, although the glycosylated haemoglobin results were moderate to small in contrast with the observed changes in weekly mean blood glucose readings which were larger. The first and second hypotheses were therefore supported since both the treatment medications were effective in the reduction of fasting blood glucose and glycosylated haemoglobin.

Results from the intergroup analysis showed there is no significant difference between the homoeopathic mother tincture and homoeopathic potency in all aspects, The null hypothesis was therefore supported since there was no difference in effect between *Syzygium jambolanum* 6CH and *Syzygium jambolanum* homoeopathic mother tincture in reducing the fasting blood glucose and glycosylated haemoglobin levels in type 2 diabetes mellitus patients on Metformin®.

From the above statements it can be concluded that *Syzygium jambolanum* (homoeopathic potency 6CH or homoeopathic mother tincture) is a successful adjunct to Metformin® in the treatment of uncontrolled type 2 diabetes mellitus.

6.2 BENEFITS OF THE STUDY

This study contributes to the body of homoeopathic knowledge in treating diabetes and complications. To date there have been no human homoeopathic research studies conducted to investigate the effect of *Syzygium jambolanum* in homoeopathic potency and mother tincture on the effect of blood glucose levels; previous research has relied on animal research studies.

Participants benefited by experiencing an improvement in the high fasting blood glucose levels associated with type 2 diabetes mellitus. Participants were educated on diabetes mellitus, the complications and the beneficial effects of lifestyle changes such as exercise and diet.

6.3 RECOMMENDATIONS

In retrospect the researcher believes that the study could be improved in the following ways:

- The true value of this remedy on HbA1c may form the topic of future research because of the moderate to small reduction in the glycosylated haemoglobin as compared to the observed changes in weekly mean blood glucose readings which were larger. Treatment effect (with respect to HbA1C) may be related to length of time on treatment
- A larger sample size should be used to secure more reliable and statistical data and would also ensure greater external validity.
- Follow-up consultations should be conducted every two weeks to ensure greater patient compliance.
- Closer monitoring of patients should be undertaken, telephonic contact should be made every week with each patient in order to ascertain compliance in terms of recording daily fasting blood glucose readings and taking the

prescribed medication as well as to reiterate that he/she must not make any dietary or exercise changes during the duration trial.

- Stratification of the patient sample with respect to the stage, severity and duration of disease should be conducted in order to ensure a homogenous group with respect to variables
- Greater flexibility with respect to potency selection and posology should be considered in future studies which would allow researchers to adapt the remedy potency according to each patient's individual sensitivity.
- Future studies should ensure that all patients are taking the same dosage as well as formulation of Metformin®.
- A simillimum study should be carried out comparing the effectiveness of the homoeopathic simillimum and a homoeopathic preparation of *Syzygium jambolanum* in the treatment of type 2 diabetes mellitus.
- Results of the study should be published.

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APPENDICES

Appendix A: Letter of information



LETTER OF INFORMATION

Dear Participant

Title of the Research Study: A COMPARISON OF THE EFFICACY OF *SYZYGIUM JAMBOLANUM* 6CH AND *SYZYGIUM JAMBOLANUM* HOMOEOPATHIC MOTHER TINCTURE IN THE TREATMENT OF TYPE 2 DIABETES MELLITUS IN PATIENTS ON METFORMIN®.

Principal Investigator/s/researcher: Pretty Mkhize (B.Tech.Homoeopathy)

Co-Investigator/s/supervisor/s: Dr Madhu Maharaj (M.Tech.Homoeopathy) and Co-supervisor Mrs J. Ducray (Medical BSc, Mmed Sci)

Brief Introduction and Purpose of the Study:

Diabetes mellitus type 2 is a chronic, progressive metabolic disease defined by the presence of hyperglycaemia. It characterised by hyperglycaemia as a result of lack of sufficient insulin production by the pancreas or an inability of the body to utilise or respond to insulin appropriately. Insulin, which is produced in the beta cells of the pancreas, is a hormone that regulates the levels of glucose within the bloodstream; hyperglycaemia may occur with uncontrolled diabetes and over a period of time can lead to long term damage to many body systems notably blood vessels, the

cardiovascular system, the kidneys and the nervous system. The purpose of this study is to compare the effectiveness of *Syzygium jambolanum* 6CH in type 2 diabetes mellitus, compared to *Syzygium jambolanum* homoeopathic mother tincture, as determined by daily fasting blood glucose and glycosylated haemoglobin levels in the treatment of type 2 diabetes mellitus in patients on Metformin®.

Outline of the procedures

The research will be conducted in the DUT Homoeopathic Day Clinic. This study aims to compare the efficacy of *Syzygium jambolanum* 6CH to the *Syzygium jambolanum* homoeopathic mother tincture in the treatment of type 2 diabetes mellitus. In order to do this I appeal to you for your assistance by becoming actively involved and informing me about your symptoms as well as their effect on your daily life. Each participant must comply with the selection criteria in order to participate in this study. The study will include those that fulfill the following criteria:

Inclusion criteria

- Participants have to be between 18 and 65 years of age
- Participants who have been previously diagnosed with type 2 diabetes mellitus and are currently taking Metformin® (Glucophage) for the treatment of diabetes.
- Participants who have a stable fasting glucose of ≥ 7.0 mmol/ L.
- Participants who are willing not to change their lifestyle or dietary habits for the duration of the trial
- Participants need to be fluent and be literate in English or Zulu

Exclusion criteria

- Participants who are pregnant or lactating during the study
- Participants diagnosed with glucose-6-phosphate deficiency
- Participants on chronic medication except for Metformin® (Glucophage).
- Participants, who are illiterate as they are required to read, understand and complete the consent form.

Screening

- Participants will be interviewed telephonically according to inclusion and exclusion criteria in order to determine if they qualify for the study. Participants will be scheduled a consultation at the Homoeopathic Day Clinic at the Durban University of Technology.

Procedure outline

The study will be conducted for a period of 14 weeks that included a 2 week baseline period followed by a 12 week treatment period.

- Visit 1 [Day 1]: a) medical and personal history taking
- b) general examination will be performed
- c) Patient will be shown how to use a Glucometer (Appendix F)

- Visit 2 [Day 15]: a) general examination will be performed
- b) treatment will be prescribed
- c) Blood will be drawn for the glycosylated haemoglobin test by a professional nurse

- Visit Day 43): a) general examination will be performed
- b) treatment will be prescribed

Visit 4 Day 70 a) general examination will be performed

-) b) treatment will be prescribed

- Visit 4 (Day 98): a) general examination will be performed
- b) analysis of average fasting blood glucose levels before and after treatment will be done.
- c) Blood will be drawn for the glycosylated haemoglobin test by a professional nurse.

Tests

- Fasting blood glucose

Patients will do a fasting blood glucose test on their own, using a Bayer Ascensia Elite Glucometer provided by the researcher every morning for a period of 98 days (12 weeks). This test involves the pricking of one's fingers.

- Glycosylated haemoglobin (HbA1C)

This test requires 8 ml of blood to be drawn. 4 ml of blood will be drawn on Visit 1 (day 1) and 4 ml of blood will be drawn on Visit 5 , 41 days after the commencement of treatment, at Isolempilo Clinic at the Durban University of Technology and taken to the Global Clinical and Viral Laboratory. The HbA1C test is an accurate reflection of the glucose control over the preceding two to three months; elevated HbA1C levels indicate poor glycaemic control and the need to adjust the patient's treatment regimen.

Risks or Discomforts to the Participant:

Participants may experience a slight discomfort when 4 ml of blood is drawn on the 2nd consultation and 5th consultation at the Isolempilo Clinic at the Durban University of Technology by a professional nurse to measure glycosylated haemoglobin (HbA1C). There have been no adverse side effects associated with consumption of *Syzygium jambolanum* and it is completely safe.

Benefits:

The direct benefit of this study is that the treatment may result in an improvement of your diabetes signs and symptoms. Your participation will increase our knowledge and understanding of the place and value of homoeopathy for type 2 diabetes mellitus treatment.

Withdrawal from the Study:

There are no known side-effects with homoeopathic treatment however a slight homoeopathic aggravation may occur in some patients, however you will be free to withdraw from this study, at any stage, and no explanation will be required.

Remuneration:

The participant will not receive any monetary or other types of remuneration.

Costs of the Study:

Participants are not expected to cover any costs related to the study.

Confidentiality:

There will be strict patient-practitioner confidentiality. Your personal details will not be disclosed at any stage of the study. All data will only be accessible to the researcher and the supervisor concerned. A qualified homoeopath is supervising the treatment and the treatment is free of charge.

Research-related Injury:

There are no known “side-effects” with homoeopathic treatment especially with low doses used in this study.

Persons to Contact in the Event of Any Problems or Queries:

In case of any queries or problems arising during the research, please feel free to contact:

Pretty Mkhize Cell number: 0791615656

Dr. M. Maharaj Tel: (031) 373 2041 (Homoeopathic Day Clinic)

The Institutional Research Ethics administrator on 031 3732900. Complaints can be reported to the DVC: TIP, Prof F. Otieno on 031 373 2382 or dvctip@dut.ac.za.

Appendix B: Consent form



CONSENT

Title of the Research Study: A COMPARISON OF THE EFFICACY OF *SYZYGIUM JAMBOLANUM* 6CH AND *SYZYGIUM JAMBOLANUM* HOMOEOPATHIC MOTHER TINCTURE IN THE TREATMENT OF TYPE 2 DIABETES MELLITUS IN PATIENTS ON METFORMIN®.

Statement of Agreement to Participate in the Research Study:

- I hereby confirm that I have been informed by the researcher **Pretty Brightness Mkhize** about the nature, conduct, benefits and risks of this study - Research Ethics Clearance Number: 1/14
- I have also received, read and understood the above written information (Participant Letter of Information) regarding the study.
- I am aware that the results of the study, including personal details regarding my sex, age, date of birth, initials and diagnosis will be anonymously processed into a study report.
- In view of the requirements of research, I agree that the data collected during this study can be processed in a computerised system by the researcher.
- I may, at any stage, without prejudice, withdraw my consent and participation in the study.
- I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared to participate in the study.

I understand that significant new findings developed during the course of this research which may relate to my participation will be made available to me.

Full Name of Participant Date Time Signature / Right Thumbprint

I **Pretty Brightness Mkhize** hereby confirm that the above participant has been fully informed about the nature, conduct and risks of the above study.

Full Name of Researcher Date Signature

Full Name of Witness (If applicable) Date Signature

Full Name of Legal Guardian (If applicable) Date Signature

Please note the following:

Research details must be provided in a clear, simple and culturally appropriate manner and prospective participants should be helped to arrive at an informed decision by use of appropriate language (grade 10 level - use Flesch Reading Ease Scores on Microsoft Word), selecting of a non-threatening environment for interaction and the availability of peer counseling (Department of Health, 2004).

If the potential participant is unable to read/illiterate, then a right thumb print is required and an impartial witness, who is literate and knows the participant e.g. parent, sibling, friend, pastor, etc. should verify in writing, duly signed that informed verbal consent was obtained (Department of Health, 2004).

If anyone makes a mistake completing this document e.g. wrong date or spelling mistake a new document has to be completed. The incomplete original document has to be kept in the participant file and not thrown away and copies thereof must be issued to the participant.

References:

Department of Health: 2004. *Ethics in Health Research: Principles, Structures and Processes*

<http://www.doh.gov.za/docs/factsheets/guidelines/ethnics/>

Department of Health. 2006. *South African Good Clinical Practice Guidelines*. 2nd Ed.

Available at:

http://www.nhrec.org.za/?page_id=14

Appendix C 1: Log sheet (glucometer reading) before intervention

LOG SHEET (GLUCOMETER READING)

Before Intervention

Day	Blood Glucose reading (mmol/ L)
1.	
2.	
3.	
4.	
5.	
6.	
7.	
8.	
9.	
10.	
11.	
12.	
13.	
14.	

Appendix C 2: Log sheet (glucometer reading) after the intervention

LOG SHEET (GLUCOMETER READING)

After the intervention

Day	Blood Glucose reading (mmol/L)
1	
2	
3	
4	
5	
6	
7	
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14	
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Appendix D: Case history

CASE HISTORY

Date:
Name:
Surname:
Age:
Gender:
Marital Status:
Children:
Occupation:
Address:
Tel:
Chief Complaint:

Past Medical History:
Surgical History:
Allergies:
Vaccination History:
Medication and Supplementation:
Family History:
Mother:
Father:
Siblings:
Grandparents: Mother's -mother:
-father:
Father's -mother:
-father:

Nutritional History:
Systems Review:
General:
Skin:
Head, Eyes, Ears, Nose, Throat:
Neck:
Breast:

Respiratory:
Cardiovascular:
Gastrointestinal:
Urinary:
Genital: Male:
Female: -menarche:
-regularity:
-frequency:
-duration of periods:
-amount of bleeding:
-menopause:
Peripheral Vascular:
Musculoskeletal:
Neurologic:

Hematologic:
Endocrine:

Appendix E: Physical examination

Date:
Name:
Surname:
Vital Signs:
Height:
Weight:
Blood Pressure:
Pulse Rate:
Respiratory Rate:
Temperature:
General Examination:
Cyanosis:
Anaemia:
Jaundice:
Clubbing:
Oedema:
Lymphadenopathy:
Dehydration:
Dyspnoea:
Eyes, Ears, Nose, Throat:

Respiratory Examination:
Cardiovascular Examination:
Abdominal Examination:
Musculoskeletal Examination:
Neurological Examination:

Appendix F: Ethics approval



Institutional Research Ethics Committee
Faculty of Health Sciences
Room M5 49, Mansfield School Site
Gate 8, Ritson Campus
Durban University of Technology
P O Box 1334, Durban, South Africa, 4001
Tel: 031 373 2900
Fax: 031 373 2407
Email: lavishad@dut.ac.za
http://www.dut.ac.za/research/institutional_research_ethics
www.dut.ac.za

10 March 2014

IREC Reference Number: REC 1/14

Ms P B Mkhize
27 Lorraine Avenue
Umbilo
4001

Dear Ms Mkhize

A comparison of the efficacy of *Syzygium Jambolanum* (Java Plum) 6CH and *Syzygium Jambolanum* (Java Plum) homeopathic mother tincture in the treatment of Type 2 Diabetes Mellitus in patients on Metformin®

I am pleased to inform you that Full Approval has been granted to your proposal REC 1/14.

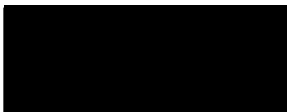
The Proposal has been allocated the following Ethical Clearance number IREC 019/14. Please use this number in all communication with this office.

Approval has been granted for a period of one year, before the expiry of which you are required to apply for safety monitoring and annual recertification. Please use the Safety Monitoring and Annual Recertification Report form which can be found in the Standard Operating Procedures [SOP's] of the IREC. This form must be submitted to the IREC at least 3 months before the ethics approval for the study expires.

Any adverse events [serious or minor] which occur in connection with this study and/or which may alter its ethical consideration must be reported to the IREC according to the IREC SOP's. In addition, you will be responsible to ensure gatekeeper permission.

Please note that any deviations from the approved proposal require the approval of the IREC as outlined in the IREC SOP's.

Yours Sincerely



PROF. K. AGAM
Chairperson: IREC

Appendix G: Advert



DIABETES MELLITUS TYPE 2

Diabetes mellitus is a condition that occurs when the body cannot use glucose normally. Glucose is the main source of energy for the body's cells. The levels of glucose in the blood are controlled by a hormone called insulin, which is made by the pancreas. Insulin helps glucose enter the cells. In diabetes, the pancreas does not make enough insulin (type 1 diabetes) or the body can't respond normally to the insulin that is made (type 2 diabetes). This causes glucose levels in the blood to rise, leading to symptoms such as increased urination, extreme thirst, and unexplained weight loss. Diabetes mellitus is a chronic disease that can cause serious health complications to the kidneys, heart, blood vessels and nervous system.

A homoeopathic research study is being conducted at the Durban University of Technology investigating potential homoeopathic treatment of Diabetes Mellitus Type 2.

You may qualify for homoeopathic treatment for Diabetes Mellitus Type 2 if:

You are between the ages 18 – 65?

You have been diagnosed with Diabetes Mellitus Type 2?

You are currently on Metformin?

If you interested in being part of this study or in case of any queries please contact:

M.Tech. Hom. Research student: Pretty Mkhize: 0791615656

Appendix H: Manufacture of *Syzygium jambolanum* 6CH

AIM: TO MANUFACTURE SYZYGIUM JAMBOLANUM HOMOEOPATHIC POTENCY

APPARATUS:

APPARATUS:

7 X 25ml Amber glass bottles
9 X 500ml Amber glass bottles
96% Alcohol
Pipettes
100ml, 1000ml beakers

METHOD

1. Using a 25ml bottle:

1CH: tincture	ROH
10/100 x vol	90/100 x vol
= 10/100 x 15	= 90/100 x 15
= 1.5ml	= 13,5ml (96%)

Mix 1.5 ml of the *Syzygium jambolanum* mother tincture and 13,5ml of alcohol in a 25 amber glass bottle, close the lid and succuss 10 times.

2. 2CH >>>>4CH

Using a 25 ml bottle:

Tincture	ROH
1/100 x vol	99/100 x vol
1/100 x 15	99/100 x 15
= 0.15 ml	= 14,85ml (96%)

Mix 0.15ml of *Syzygium jambolanum* 1CH and 14,85ml of 96% alcohol in a 25ml amber glass bottle, close the lid and succuss 10times

3. 5CH

Using a 100ml bottle:

Tincture	ROH
$1/100 \times \text{vol}$	$99/100 \times \text{vol}$
$1/100 \times 70$	$99/100 \times 70$
= 0,7ml	= 69.3ml (96%)

Mix 0.7ml of *Syzygium jambolanum* 4CH and 69.3ml of 96% alcohol in a 100ml amber glass bottle, close the lid and succuss 10 times

4. According to calculations 3 Liters of *Syzygium jambolanum* would be sufficient for the duration of the study.

6CH

Tincture (5CH)	ROH
$1/100 \times \text{vol}$	$99/100 \times \text{vol}$
$1/100 \times 3000$	$99/100 \times 3000$
= 30ml (5CH)	2970ml (30% ROH)

5. For accuracy lab technician suggested researcher uses nine 500ml bottles as follows:

500ml bottles

6CH

$1/100 \times \text{vol}$	$99/100 \times \text{vol}$
$1/100 \times 350$	$99/100 \times 350$
= 3.5ml (5CH)	=346, 5 ml (30% ROH)

Mix 3.5ml of the tincture and 346.5ml in a 500 ml bottle, close the lid and succuss 10 times.

Appendix I: Instructions on how to perform the blood glucose test

INSTRUCTIONS ON HOW TO PERFORM THE BLOOD GLUCOSE TEST

Preparations for the Blood Glucose Test

1. Load the Lancing Device. (Place the Lancing Device on a clean surface while preparing for your Blood Glucose Test)
2. Wash your hands. Use warm soapy water. Rinse and dry thoroughly.
3. Remove foil packets from carton and tear off a single packet.
4. To open the test strip packet peel the foil until the test strip is completely exposed.
5. Remove the Test Strip from packet. Holding the round end, insert the Test strip fully into the meter. (Be sure to save the foil use when disposing of the Test Strip). A beep sounds and a full display appears, followed by the function number (F#) and the previous test result. The previous test result. The previous test result begins flashing alternatively.

(Ascensia Elite User Guide, 2002: 17-19)

How to perform the Blood Glucose Test

1. Prick your finger with a lancet or Automatic Lancing Device and press the finger to form a small drop of blood.
2. Touch and hold the test end (tip) of the Test Strip to the drop of blood until the reaction chamber is completely filled and meter beeps. You may now use a tissue or cotton ball for wiping the finger that was pricked.
3. After 29 seconds, your blood glucose result appears in the display. The test result remains in the display for 3 minutes. (You must record your Fasting blood glucose reading on the Log Sheet provided).

CAUTION: Use a tissue to remove the Test Strip. Dispose of the used Test Strip and lancet carefully to prevent injury or contamination to others. Remember to use the empty foil packet to dispose of the test strip.

(Ascensia Elite User Guide, 2002: 20-21)

Appendix J: Certificate of Analysis of Syzygium jambolanum mother tincture

Gehrlicher

Pharmaceutical Extracts GmbH

Certificate of analysis

Name of the product:	Syzygium jambolanum - Mother Tincture
Lot-No.:	U 4012
Botanical name:	Syzygium cumini (L.) Skeels.
Plant section used:	Dried fruits
Extract medium:	Ethanol 62 % m/m according to rule 4 a Ph. Eur. 2011 / HAB 2011
Appearance:	ethanolic, clear solution Colour: brownyellow Odour: aromatic
Identity (TLC):	according to HAB 2010 complies
Relative density Ph. Eur. 2011:	0,8977
pH Ph. Eur. 2011:	5,2
Dry residue Ph. Eur. 2011:	2,0 % m/m
Methanol/Isopropylalcohol (GC):	complies, according to Ph. Eur. 2011 ($\leq 0,05$ % V/V)
Ethanol content (Ph. Eur. 2011):	67,4 % V/V = 59,7 % m/m
Spectrum UV-VIS: (methanolische Lösung)	documented Journal-No.: brown 183
Manufacturing date:	01/2014
Expiry date:	01/2019

July 14th, 2014 - Be/SB



Gehrlicher
Pharmazeutische Extrakte
AZ-ENGL/URTINKTUREN/Urtinkturen H_Z.doc

Gehrlicher, Pharmazeutische Extrakte GmbH, Robert-Koch-Straße 5, D-82547 Eurasburg/Obb., Telefon: 08179/99779-0, Telefax: 08179/99779-69