IN VIVO HYPOGLYCEMIC ACTIVITY AND SAFETY OF SELECTED MEDICINAL PLANTS USED IN THE MANAGEMENT OF DIABETES MELLITUS IN ELGEIYO-MARAKWET COUNTY, KENYA

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OCTOBER 2019

DECLARATION

I, DINAH JEMELI SAWE, duly declare that this thesis is my original work and has not been presented for a degree in any other university or for any other award

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DEDICATION

I hereby dedicate this thesis to my two daughters Faith Jerotich and Luizza Chepkemboi, to whom am very grateful for their understanding and encouragement during times when I was away.

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ACRONYMS AND ABBREVIATIONS

EDTA	Ethylene Diamine Tetra- Acetic Acid
EDXRF	Energy Dispersive X-Ray Fluorescence
FPG	Fasting plasma Glucose
GDM	Gestational Diabetes Mellitus
GFR	Glomerular Filtration Rate
HB	Hemoglobin
HB	Hemoglobin
AAS	Atomic Absorption Spectrophotometry
ADA	American Diabetes Association
ADM	American Diabetic Management
ALP	Alkaline Phosphatase
ALT	Aspartate Amino Transfarase
AMY	Amylase
ANOVA	Analysis of Variance
AST	Aspartate Amino Transfarase
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CDC	Centre for Disease Control
Cr	Chromium
CREAT	Creatinine
DBIL	Direct Bilirubin
DM	Diabetes Mellitus
HCL	Hydrochloric Acid
$HClO_4$	Perchloric Acid
HDL- C	High Density Lipoprotein
HNO_3	Nitric Acid
IFG	Impaired Fasting Glycemia
IGT	Impaired Glucose Tolerance
IU	International Unit

IU	International Units
LDL-C	Low Density Lipoproteins
MCH	Mean Cell Hemoglobin
MCH	Mean Cell Volume
MCHC	Mean Cell Hemoglobin concentration
MCV	Mean Cell Volume
Mg	Magnesium
mMol/L	Milimoles per liter
NAD	Nicotinamide Adenine dinucleotide
OGTT	Oral Glucose Tolerance test
PCV	Packed Cell Volume
RBC	Red Blood Cell
SEM	Standard Error of Mean
TBIL	Total Bilirubin
TCHO	Total Cholesterol
TG	Triglycerides
TRXF	Total Reflection X-Ray Fluorescence
TXRF	Total X-ray Fluorescence Spectroscopy
U.S	United States
U.S.A	United States of America
V	Vanadium
WBC	White Blood Cell
W H O	World Health Organization

ABSTRACT

Diabetes Mellitus is a group of metabolic disorders sharing a common underlying feature of hyperglycemia with disturbances of carbohydrate, protein and fat metabolism. The disease may present with characteristic symptoms such as polydipsia, polyuria, polyphagia, blurring of vision, and weight loss and in its most severe forms, ketoacidosis or a non-ketotic hyperosmolar state may develop and lead to stupor, coma and, in absence of effective treatment, death. Hyperglycemia may be as a result of defects in insulin secretion, insulin action or both. The use of conventional antidiabetic drugs may have adverse effects including hematological, cutaneous and gastrointestinal reactions, hypoglycemic coma, flatulent, diarrhea and impairment of liver and kidney functions. Some do not lower blood sugar when used alone and require combination therapy. The aim of this study was to determine the antidiabetic activity and safety in a rat model of five plants, *Maerua subcordata* (Gilg) De Wolf, *Chasmanthera dependens* Hochst, *Pappea capensis* Spreng, S*yzigium cordatum* and *Mayrtenus undata* (Thumb) traditionally used to manage diabetes mellitus (DM). The plant parts were collected, dried, crashed into fine powder, extracted using distilled water at 60^{o}C and lyophilized using a Freeze Dryer, packaged in air tight containers and stored at -20^{o}C ready for use. The extracts were orally and intraperitoneally screened in alloxan induced diabetic mice for their hypoglycemic activity at doses of 25, 48.4, 93.5, 180.9 and 350 mg/kg body weight. Diabetes in mice was induced using 186.9 mg/kg body weight of alloxan monohydrate. Negative controls included normal and diabetic mice orally and intraperitoneally administered with physiological saline while positive controls included diabetic rats administered with glibenclamide as oral and insulin as intraperitoneal reference drug. The safety of the extracts was studied in mice orally and intraperitoneally administered with 450, 670, and 1000 mg/kg body weight daily for 28 days by recording the changes in body and organ weight, hematological and biochemical parameters and histopathology. Mineral composition of the extracts was estimated using total reflection X-ray fluorescence system (TRXF) and atomic absorption spectroscopy while the types and quantities of phytochemicals present were assessed using standard procedures. Results revealed hypoglycemic activity in three out of the five studied plants at the five different doses when given either orally or intraperitoneally. Results revealed significant difference between the control and experimental mice on total white blood cell and differential white blood cell count, RBC, PCV, Hb, MCV in mice models treated with *Maerua subcordata* and *Mayrtenus undata*, α-AMYL in those treated with *Syzigium cordatum* and *Pappea capensis* and TC and LDL-C in *Chasmanthera dependens* extract treated mice. There was significant loss of body weight and loss or gain of organ weights. At tissue level, there was accumulation of inflammatory cells in mice treated with *P. capensis* and in mice treated with high doses of *Mayrtenus undata* and *Chasmanthera dependens*. Phytochemicals present included saponins, flavonoids, alkaloids, tannins and total phenols. All the analyzed trace elements were within the recommended daily allowance RDA) except for Manganese in *P. capensis*. In conclusion, the studied plants exhibited safe hypoglycemic activity which was contributed by the phytochemicals and mineral elements present in these plants extracts. The study recommends continued use of the three studied plant extracts at low doses. Similar studies should be carried out using higher animals including man.

CHAPTER ONE

INTRODUCTION

1.1 Background Information

Diabetes mellitus is a group of metabolic disorders sharing a common underlying feature of hyperglycemia with disturbances of carbohydrate, protein and fat metabolism. The disease may present with characteristic symptoms such as polydipsia, polyuria, polyphagia, blurring of vision, and weight loss and in its most severe forms, ketoacidosis or a non-ketotic hyperosmolar state may develop and lead to stupor, coma and, in absence of effective treatment, death (ADA, 2007). During onset, symptoms may not be present and consequently hyperglycemia sufficient to cause pathological and functional changes may be present for a long time before the diagnosis is made. Hyperglycemia may be as a result of defects in insulin secretion, insulin action or both. The chronic state and attendant metabolic disturbances may be associated with secondary damage in multiple organ systems, especially the kidneys, eyes, nerves, and blood vessels resulting to coronary heart disease and cerebrovascular disease (Virella *et al.,* 2003). Prevalence of diabetes mellitus for all age groups was estimated to be 422 million people in 2014 and is projected to be the seventh leading cause of death in 2030 according to global report on diabetes (WHO, 2016). Almost half of the deaths attributable to high blood sugar occur before the age of 70 years.

Management of diabetes mellitus can be achieved through the oral antidiabetic agents like sulfonylureas, biguanides, meglitinede, D-phenylalanine derivatives, and alpha-

glucosidase inhibitors among others or the intraperitoneal form, insulin. The use of oral antidiabetic drugs is limited due to their adverse effects including hematological, cutaneous and gastrointestinal reactions, hypoglycemic coma, flatulent, diarrhea and impairment of liver and kidney functions (WHO, 2002). Some do not cause low blood sugar when used alone and require combination therapy.

Plants have always been a good source of drugs. Ethnobotanical survey shows that about 800 plants may possess anti-diabetic potential (Patel *et al*., 2011). Several plants have been used as dietary adjuvant and in treating a number of diseases even without knowledge on their proper functions and composition. Metformin, a less toxic biguanides and a potent oral glucose-lowering agent, was developed from *Galega officianalis* and is used in treatment of diabetes (Jerald *et al.,* 2011). Studies have revealed that aqueous stem bark extracts of some plants have potent hypoglycemic activity in alloxan-induced diabetic mice (Njagi *et al.,* 2012).

Extracts from the stem barks and roots of *Maerua subcordata, Chasmanthera dependens, Pappea capensis, Syzigium cordatum, Mayrtenus undata (Thumb.)* are gaining popularity in the management of hyperglycemia, bacterial, fungal and some viral infections and therefore there is need to evaluate efficacy and safety of these plants extracts and provide scientific knowledge to the many diabetic cases opting to traditional medicine (Zakaria *et al*., 2007).

1.2 Statement of the Problem and Justification

Diabetes mellitus is a great challenge in the health sector and a socio-economic growth impediment worldwide. Its complications are life threatening and the increasing number of people suffering from it face a number of challenges from the current antidiabetic agents in terms of cost and side effects like hypoglycemia, hematological, gastrointestinal disturbances and nausea. *Maerua subcordata, Chasmanthera dependens, Pappea capensis, Syzigium cordatum* (Lamaiwet) and *Mayrtenus undata* (Miraa) are gaining popularity in Keiyo South, Kenya in the management of diabetes mellitus as an alternative medicine; however, their efficacy and long term safety have not been scientifically evaluated. There is therefore need to determine efficacy and safety of their use in management of diabetes.

1.3 Null Hypotheses

- ✓ Aqueous extracts of *Maerua subcordata, Chasmanthera dependens, Pappea capensis, Syzigium cordatum* and *Mayrtenus undata (Thumb.)* at therapeutic doses have no significant *in vivo* hypoglycemic activity on alloxan induced diabetic male albino mice
- ✓ Aqueous extracts of *Maerua subcordata, Chasmanthera dependens, Pappea capensis, Syzigium cordatum* and *Mayrtenus undata (Thumb.)* at high non-therapeutic doses are unsafe on normal control male albino mice.
- ✓ Aqueous extracts of *Maerua subcordata, Chasmanthera dependens, Pappea capensis, Syzigium cordatum* and *Mayrtenus undata (Thumb.)* do not possess

mineral elements and phytochemicals associated with hypoglycemic activity and safety.

1.4 General Objective

To evaluate *in vivo* hypoglycemic activity and safety of aqueous extracts of *Maerua subcordata, Chasmanthera dependens, Pappea capensis, Syzigium cordatum* and *Mayrtenus undata* on alloxan induced diabetic male albino mice.

1.4.1 Specific Objectives

i) To determine *in vivo* hypoglycemic effects of oral and intraperitoneal administration of aqueous extracts of *Maerua subcordata, Chasmanthera dependens, Pappea capensis, Syzigium cordatum* and *Mayrtenus undata* to alloxan induced male albino mice at therapeutic doses.

ii) To assess the effects of oral and intraperitoneal administration of aqueous extracts of *Maerua subcordata, Chasmanthera dependens, Mayrtenus undata, Pappea capensis* and *Syzigium cordatum* to normal control mice daily for 28 days at high non-therapeutic doses

iii) To determine the mineral and phytochemical composition of aqueous extracts of *Maerua subcordata, Chasmanthera dependens, Pappea capensis, Syzigium cordatum* and *Mayrtenus undata.*

CHAPTER TWO

LITERATURE REVIEW

2.1 Definition of Diabetes mellitus

Diabetes mellitus (DM) is a clinical syndrome characterized by hyperglycemia due to absolute or relative deficiency of insulin (Sukha and Rubin, 2007). Deficiency in insulin production by the pancreas or inability of the insulin produced to bind effectively to its receptor on the cell surface results to chronic hyperglycemia and the attendant metabolic disregulation may be associated with secondary damage in multiple organ systems, especially the .kidneys, eyes, nerves, and blood vessels (Virella *et al.,* 2003). Insulin has several functions in the human body. In the liver insulin increases the storage of glucose as glycogen. This involves the insertion of additional GLUT2 glucose transport molecules in cell plasma membranes.

In the muscle, insulin stimulates glycogen and protein synthesis. Glucose transport into muscle cells is facilitated by insertion of additional GLUT4 transport molecules into cell plasma membrane. In adipose tissue, insulin facilitates triglyceride storage by activating plasma lipoprotein lipase, increasing glucose transport into cells via GLUT4 transporters and reducing intracellular lipolysis (Jagessar *et al.,* 2015).

The primary symptoms are hyperglycemia and glucosuria, polyuria, polydipsia and polyphagia, sudden weight loss, ketonuria and ketonemia in acute episodes which results from inability to regulate glucose metabolism (Brownlee, 2001). In the later stage of diabetes, lipid metabolism is affected and is seen as hyperlipidemia and

hypercholesterolemia, a risk factor in atherosclerosis (Ross, 1999; Schwartz, 2006; WHO, 2006).

Insulin deficiency may arise in various ways such as destruction of β-cells of the pancreas, an organ responsible for the production of insulin (Leslie *et al*., 2008) and although the exact cause of the disease is uncertain, genetic and secondary predisposing factors contribute to the onset of the disease (Shafee *et al*., 2008). Any other abnormality in the glucose metabolism pathway may result in hyperglycemia.

2.2 Epidemiology of diabetes mellitus

Diabetes mellitus and its complications constitute a significant public health problem worldwide and an important cause of morbidity and mortality. Increase in obesity rates is to blame for much of the increase especially of type 2 DM. In the USA, two thirds of the adults are reported to be overweight or obese, and as a result, predictions show that one in three US citizens born in 2000 will develop diabetes mellitus. Habits characterized by low daily energy expenditure daily and by excessive ingestion of foods rich in carbohydrates and lipids, result in positive energy balance leading to increase of the body mass index (BMI) and prevalence of obesity in developed as well as developing countries (Mukundi *et al*., 2015).

2.3 Classification of Diabetes mellitus

Previous classification schemes of diabetes mellitus were based on the age at onset of the disease or on the mode of therapy (WHO, 1985). In contrast, the recent revised

classification reflects the greater understanding of the pathogenesis of each variant (WHO, 1997). The vast majority of cases of diabetes fall into one of 3 broad classes: Type I diabetes mellitus is characterized by loss of the insulin-producing beta cells of the islets of Langerhans in the pancreas leading to insulin deficiency. This type of diabetes can be further classified as immune-mediated or idiopathic (ADA, 2007). The majority of type I diabetes is of the immune-mediated nature, where beta cell loss is a T-cell mediated autoimmune attack. The HLA genes encode proteins called major histocompatibility complex (MHC), and there are two main classes of MHC proteins, both of which display chains of amino acids. The chains are called antigens, and immune cells (called T cells) analyze them. MHC class 1 present chains from inside the cells, whereas MHC class 2 present chains from outside the cells. If T cells bind to the chain presented on an MHC, the T cell immediately orchestrates powerful attacks by the body's other immune cells (ADM, 2007). Ideally, the body only contains T cells that bind to chains from infectious organisms (Viruses, bacteria, etc.) and tumor cells. The alternative is found in autoimmune diseases such as diabetes where T cells bind to chains from the body's healthy cells.

There are many different alleles of the HLA genes, leading to many different variants of MHC proteins and allowing a variety of chains to be presented to cells. The inheritance of particular HLA alleles can account for over half of the genetic risk of developing type 1 diabetes (Frier and Fisher, 2010). The genes encoding class II MHC proteins are most strongly linked with diabetes, and these genes are called HLA-DR, HLA-DQ, and HLA-DP. There is no known preventive measure against type 1 diabetes, which causes

approximately 10 % of diabetes mellitus cases in North America and Europe. Sensitivity and responsiveness to insulin are usually normal, especially in the early stages. Type I diabetes can affect children or adults but was traditionally termed "juvenile diabetes" because it represented a majority of the diabetic cases in children (WHO, 1999).

Diabetogenic agents such as chemicals, biological agents, peptides, potentiators and steroids are known to induce diabetes. Alloxan is an oxygenated pyrimidine and toxic analog of glucose. Alloxan destroys β cells and is used in research models to induce diabetes. It selectively destroys insulin-producing cells in the pancreas when administered to rodents and many other animal species. This compound does not affect human cells. It causes an insulin-dependent diabetes mellitus (called "alloxan diabetes") in these animals, with similar characteristics to type 1 diabetes in humans. It preferentially accumulates in beta cells through uptake via the GLUT2 glucose transporter (Danilova, 2014).

Alloxan, in the presence of intracellular thiols, generates reactive oxygen species (ROS) in a cyclic reaction with its reduction product, dialuric acid. The beta cell toxicity action is initiated by free radicals formed in this redox reaction. The selective uptake of the compound is due to its structural similarity to glucose as well as the beta-cell's highly efficient uptake mechanism (GLUT2). In addition, alloxan has a high affinity to SH-containing cellular compounds and, as a result, reduces glutathione content. In addition, alloxan inhibits glucokinase, a SH-containing protein essential for insulin secretion

induced by glucose (Szkudelski, 2001). Some studies have shown that alloxan is not toxic to the human beta-cells, even in very high doses, probably because of differing glucose uptake mechanisms in humans and rodents (Tyrberg *et al.*, 2001, Lenzen 2008). It is, however, toxic to the liver and the kidneys in high doses.

Type II diabetes is caused by a combination of peripheral resistance to insulin action and an inadequate secretory response by the pancreatic β-cell (relative insulin deficiency). Approximately 80 % to 90 % of diabetic patients have type 2 diabetes, while variety of monogenic and secondary causes are responsible for the remaining cases (WHO, 1999).

Gestational diabetes mellitus (GDM), defined as any degree of glucose intolerance that is first recognized during pregnancy and affects approximately 4 % of all pregnancies. GDM generally resolves postpartum, although women who have experienced gestational diabetes are at higher risk of developing type 2 diabetes mellitus (ADM, 2007). Hormones produced during pregnancy causes insulin resistance that is normally compensated for by increased insulin secretion. Similar to individuals with type 2 diabetes, women with GDM are unable to meet the increased demand for insulin due to an underlying insulin secretory defect (Beaser, 2001). Despite major types of diabetes having different pathogenic mechanism, the long - term complications in kidneys, eyes, nerves and blood vessels are the same, as are the principle causes of morbidity and death.

Other types include impaired glucose tolerance (IGT) and impaired fasting glycaemia (IFG). IGT and IFG are intermediate conditions in the transition between normality and diabetes. People with IGT or IFG are at high risk of progressing to type 2 diabetes although this is not inevitable. Obesity has been associated with insulin resistance which precedes type 2 diabetes mellitus. Insulin stimulates production of leptin when adipocytes are exposed to glucose to encourage satiety while leptin via negative feedback decreases the secretion of insulin (Carey *et. al*., 1997).

2.4 Diagnosis of Diabetes mellitus

Diabetes Mellitus is a disease which may complicate and affect all organ systems in the body. Prevention, timely diagnosis, and treatment are important in patients with diabetes mellitus. Many of the complications associated with diabetes, such as nephropathy, retinopathy, neuropathy, cardiovascular disease, stroke, and death, can be delayed or prevented with appropriate treatment by controlling elevated blood pressure, lipids, and blood glucose (Albert *et al*., 1998).

The body, under normal circumstances, is able to keep glucose concentrations stable within the range of 4-7 mmol/L. The normal fasting blood sugar is usually between 2-5 mmol/L. After a meal it would rarely exceed 8.0 mmol/L. In normal condition, there is no glucose in urine since the normal threshold above which glucose would appear in the urine would be 10 mmol/L. Any value below a concentration of 10 mmol/L allows the kidneys to reabsorb glucose back into the blood stream and so glucose does not appear in the urine unless the blood concentration of glucose is high (Ta *et al*., 2014).

The criterion of diagnosis of diabetes mellitus is based on presence of signs and symptoms and on three major laboratory findings according to ADA, (2012).

a) A fasting plasma glucose test of ≥ 90 mg/dL (5.0 mmol/L)

Blood glucose is measured after 8 to 14 hrs of fasting preferably after an overnight fast.

b) Oral Glucose Tolerance Test (OGTT) of 200 mg/dL (11.1 mmol/L) 2 hours after glucose load

The oral glucose tolerance test evaluates clearance from the circulation after glucose loading under defined and controlled conditions (Mari *et a*l., 2001). The patient needs to have been fasting 8 to 14 hours prior to sampling. Before oral administration of the glucose solution within 5 minutes, a zero time (baseline) blood sample is drawn. Blood is then drawn at 1-hour intervals for the next 2hrs for measurement of glucose, and sometimes insulin levels. In a non-diabetic, the blood glucose level increases immediately after a high sugar or carbohydrate drink and then decreases gradually since high blood sugar levels stimulates insulin release from the beta cells that enhances uptake of glucose by peripheral tissues from the blood stream resulting to its low levels (Tietz, 2002). In a diabetic, the glucose in the blood continues to go up and stays high after drinking the sweetened liquid. Therefore, a plasma glucose level of 200 mg/dL or higher at two hours after drinking the sweetened syrup and at one other point during the two hour test period confirms the diagnosis of diabetes mellitus (Ta, 2014).

c) Glycosylated hemoglobin value of 6.5% indicates diabetes.

Pre-diabetes individuals present with values of 5.7 % to 5.99 %. Normal glucose levels give values less than 5.7 %. In diabetes mellitus, a minor hemoglobin derivative called HbA1c is produced by glycosylation. Since this reaction is spontaneous and erythrocytes are completely permeable to glucose, the quantity of HbA1c formed is directly proportional to the average plasma glucose concentration that the erythrocytes are exposed to during their 120-day life span (4 to 6 weeks before sampling) (Selvin *et al*., 2010).

For normoglycemic persons, HbA1c constitutes 4 to 5 % of total hemoglobin whereas in diabetics, HbA1c levels are significantly elevated. The elevations are directly proportional to the long-term degree of hyperglycemia. Glycosylated hemoglobin is most useful in monitoring diabetes mellitus. However, they are not sufficiently sensitive to effectively detect borderline cases of diabetes mellitus. Serum albumin is also glycosylated to a degree proportional to plasma glucose levels. The short half-life for albumin of 15 days makes it a good monitor of short-term blood plasma glucose levels (Selvin *et al*., 2010).

d) Intravenous glucose tolerance test

The intravenous glucose tolerance test is used for persons with malabsorptive disorders or previous gastric or intestinal surgery. Glucose is administered intravenously over 30 minutes, using a 20 % solution. A glucose load of 0.5 g/kg of body weight is used. Non-diabetics respond with plasma glucose level of 11.1-13.9 mmol/L. Discontinuation of

the glucose loading leads to a decrease in plasma level with fasting levels reached at about 90 minutes. Diabetics demonstrate plasma glucose level of 13.9 mmol/L and above during administration of the load. On discontinuation of the loading, plasma glucose levels of diabetics also return to fasting levels at about 90 minutes. An alternative procedure called the Soskin method uses 50 % glucose delivered intravenously within 3 to 5 minutes. The glucose load used is 0.3 g/kg of body weight. Non-diabetics re-establish fasting levels in less than 60 minutes after discontinuing the glucose infusion. In diabetics fasting levels are established significantly later than 60 minutes (Dods, 2010).

e) O'Sullivan-Mahan glucose challenge test

O'Sullivan-Mahan glucose challenge test is used frequently to detect gestational diabetes. A 50g load of glucose is given to a fasting patient and a blood glucose measurement is made 1 hour after dosage. A plasma glucose value of above 7.8 mmol/L suggests gestational diabetes, and a full oral glucose tolerance test is recommended for such patients (Dods, 2010).

f) Plasma insulin test

Fasting plasma insulin levels in type I diabetics are usually low. Those of type II diabetics are low only when fasting plasma glucose levels exceed 13.9 mmol/L otherwise, they are normal or even elevated. A glucose challenge separates type I diabetics from type II diabetics. Glucose loading elicits no significant insulin response

for type I diabetics and a delayed, exaggerated response in type II diabetics (Dods, 2010).

g) Urine tests

Urine tests are undertaken to analyze glucose, ketone bodies, and proteins in the urine (Piero *et al.*, 2012b). Testing urine for glucose with dipsticks is a common screening procedure for detecting diabetes. If possible, testing should be performed on urine passed 1-2 hours after a meal to maximize sensitivity (Frier and Fisher, 2010). However urinary glucose is a poor marker for diabetes. The normal renal threshold for glucose is 10 mmol/L. Blood glucose levels must exceed this value before excessive glucose is apparent in the urine. Further complicating this picture is the fact that the renal threshold in persons with diabetes often is increased to levels above 16.7 mmol/L (Dods, 2010).

2.5 Complications of Diabetes Mellitus

2.5.1 Diabetic ketoacidosis and hyperosmolar hyperglycemic nonketotic syndrome

These conditions represent decompensation in diabetic control and require immediate treatment. Careful evaluation of the patient for associated or precipitating events must be undertaken, for example infection, medical and vascular events and the associated problems must be treated (ADA, 1999).

2.5.2 Diabetic retinopathy

Diabetic retinopathy can result into any level of macular edema, severe non-proliferative retinopathy or any proliferative retinopathy and these requires prompt care of an ophthalmologist.

It is a serious micro-vascular complication of diabetes and a leading cause of visual impairment in people with diabetes. WHO estimates that diabetic retinopathy accounts for approximately 5 % of the global prevalence of blindness with estimates of 15-17 % in developed countries (Lee *et al.*, 2010; Nwaobi, 2011). It is reported to be the leading cause of blindness in people aged 20-74 years in industrialized nations (Jabbour *et al.*, 2008). Studies have established that duration of type 1 diabetes is the best predictor of developing diabetic retinopathy. Evidence suggests that hyperglycemia is the primary cause of diabetic retinopathy

2.5.3 Diabetic nephropathy

The earliest stage of diabetic nephropathy is persistent microalbuminuria at range of 30-299 mg/24hr and is a significant risk marker for cardiovascular disease. This can likely progress to clinical albuminuria (>300mg/24hr) and decreasing GFR over a period of years. It has been classically defined by the presence of proteinuria (> 0.5 g/24h) or persistent albuminuria (> 300 mg/24hr) (Osiogo *et al.*, 2006). Incidence of diabetic nephropathy is about 1-2 % per year in patients with type 1 DM. Recent studies have shown substantial reduction in incidence of diabetes nephropathy in type 1 DM. The decline is attributed to the adoption in clinical practice of measures that contribute to

early diagnosis and prevention of the disease. There is a marked racial, ethnic and international disparity in the epidemiology of diabetic nephropathy (Jabbour *et al.,* 2008). These disparities have been extensively reported in the United States, with African Americans having the highest reported incidence and prevalence of treated end stage renal disease (Gheith *et al*., 2016).

2.5.4 Neuropathy

Peripheral diabetic neuropathy may result in pain, loss of sensation and muscle weakness. Autonomic involvement can affect gastrointestinal, cardiovascular and genitourinary functions. It is a condition that is associated with nerve damage**.** Diabetic neuropathy can be classified as peripheral, autonomic, proximal or focal, depending on the affected body part, focal neuropathy is the less prevalent and is generally acute and self-limiting (Jabbour *et al.,* 2008; Moura *et al.,* 2013). Peripheral neuropathy is the most common manifestation with chronic sensor motor symptoms and signs, the onset of which is usually insidious, it may be asymptomatic in about 50 % of patients, 10 % to 20 % of patients may have sensory symptoms necessitating treatment (Smith *et al.,* 2012). Diabetic neuropathy is more frequent in older people, on average neuropathy symptoms begin to appear within 10 –20 years of the diagnosis of diabetes, and approximately 50% of diabetic patients will develop nerve damage (Moura *et al.,* 2013**).**

Neuropathy is the most common cause of foot ulcers in diabetic population, and it is associated with increased likelihood of amputations especially in western countries (Llorente and Malphurs, 2007). Diabetic neuropathies develop as a result of

hyperglycemia which inhibits the normal uptake of myoinositol, leading to a decrease in the myoinositol within the nerve. This action prolongs nerve conduction, causing nerve dysfunction. Long-term hyperglycemia also activates the polyol pathways (Xu *et al.,* 2012). The excess glucose is converted to sorbitol and fructose, causing the accumulation of sorbitol and fructose in nerve cell. Their accumulation leads to intracellular osmotic stress (Xu *et al.*, 2012).

2.5.5 Diabetic foot

Foot infection involving the skin and soft tissues is a common complication of diabetic individuals and represents a major cause of morbidity and mortality and is a major reason for lower-limb amputation (Crouzet *et al*., 2011). The feet of diabetic patients become susceptible to both ischemic and neuropathic ulceration. Neuropathic ulceration is the consequence of traumatic damage to the skin in the presence of sensory loss, especially when accompanied by mechanical derangement of the foot (Scobie, 2002).

The estimated annual total cost of diabetes related to foot complications in the UK is approximately $252 million inclusive of $8459 for every single amputation (Paton *et al*., 2011). Patients with diabetes have a 12-25 % life time risk of developing foot ulcers. Major amputations are done when the ulcerated foot either threatens patient survival or when reasonable function can no longer be expected (Leung, 2007).

2.5.6 Dyslipidemia

Diabetes increases the risk of atherosclerotic vascular disease. A common abnormal lipid pattern in such patients is an elevation of VLDL, a reduction in HDL and an LDL fraction that contains a greater proportion of small dense LDL particles (American Diabetes Association, 2001).

2.5.7 Hypertension

Hypertension contributes to the development and progression of chronic complications of diabetes mellitus. In type 1 diabetes mellitus, persistent hypertension is often a manifestation of diabetic as indicated by concomitant elevated levels of urinary albumin and in later stages by a decrease in glomerular filtration rate (GFR). Isolated systolic hypertension may occur with long duration of either type of DM due to inelasticity of atherosclerotic large vessels (ADA, 2001). Control of hypertension has been demonstrated conclusively to reduce the rate of progression of diabetic nephropathy and to reduce the complications of hypertension nephropathy, cerebrovascular disease and cardiovascular disease (ADA, 2001).

2.5.8 Psychiatric disorders

Schizophrenia is a chronic psychiatric disorder, characterized by abnormalities in thinking, emotions and behavior. Studies have found association between schizophrenia and diabetes. Reasons given for the increased risk for type 2 diabetes mellitus in this population include inadequate healthcare, less healthy lifestyle and side effects of antipsychotics (Llorente and Malphurs, 2007). Also, stigma associated with serious

mental illness as well as general medical community's discomfort and fear related to working with patients who have serious mental illness render such patients unwelcome in medical clinics and thus influence the care they receive. Schizophrenia may thus be considered an independent risk factor for diabetes mellitus (Jabbour *et al.,* 2008). People with schizophrenia are more likely than the general population to be overweight and obese even before the age of antipsychotic treatments. Use of both typical and anti psychotic medications has been associated with weight gain and glucose intolerance (Jabbour *et al.,* 2008).

Depression symptoms have negative impact on symptom burden, functional impairment, adherence to medication regimens and self management of illness (Llorente and Malphurs, 2007). Evidence has shown that persons with diabetes and depression symptoms have mortality rates nearly twice as high as persons with diabetes and no depression symptoms (Llorente and Malphurs, 2007*).*

Cognitive impairment: Diabetes mellitus also increases the risk of cognitive impairment, a process that affects the deposition of amyloid beta (Aβ) in the brain, which is the putative culprit in the pathogenesis of Alzheimer's disease (AD) (Llorente and Malphurs, 2007). Diabetes mellitus increases cognitive impairment which raises concerns about the ability of persons with this disorder to follow proper treatment. There is evidence to suggest that better diabetes treatment control improves recognition (Llorente and Malphurs, 2007).

2.5.9 Sexual dysfunction

Both physiological and psychological factors can contribute to sexual dysfunction among patients with diabetes mellitus. Normal human sexual activity is composed of four stages; desire, arousal, orgasm and resolution. Sexual dysfunction is prevalent among men with diabetes occurring two to four times more often than in persons without diabetes. Whereas sexual dysfunction most commonly develops after the age of 60 years, it tends to occur 5-10 years earlier among men with diabetes. Diabetes may affect arousal due to decreased genital sensation and lubrication. Women with type two diabetes mellitus are also predisposed to vaginal dryness and infections which can lead to dyspareunia (Llorente and Malphurs, 2007*).*

2.6 Management of Diabetes mellitus

Management of diabetes mellitus has been achieved through oral and intraperitoneal agents. The primary aim of the treatment is to save life and alleviate symptoms. Secondary aims are to prevent long-term diabetic complications and, by eliminating various risk factors, to increase longevity. Insulin replacement therapy is the mainstay for patients with type 1 DM while diet and lifestyle modifications are considered the corner stone for the treatment and management of type 2 DM. Insulin is also important in type 2 DM when blood glucose levels cannot be controlled by diet, weight loss, exercise and oral medications.

Oral hypoglycemic agents including sulphonylureas, biguanides, alpha glucosidase inhibitors and thiazolidenediones have been successfully used in the management of

DM. The main objective of these drugs is to correct the underlying metabolic disorder, such as insulin resistance and inadequate insulin secretion. They are prescribed in combination with an appropriate diet and lifestyle changes to reduce weight, improve glycaemic control and reduce the risk of cardiovascular complications, which account for 70 to 80% of deaths among those with diabetes. Diabetes is best controlled either by diet alone and exercise (non-pharmacological), or diet with herbal or oral hypoglycemic agents or insulin (Bastaki, 2005; ADM, 2012).

2.6.1 Insulin Therapy

Insulin is the cornerstone of pharmacotherapy in persons with type 1 DM. Progressively more aggressive targeted glycemic, blood pressure, and LDL cholesterol treatment strategies impact both micro-vascular and macro-vascular diabetes complications and co-morbidities (Jabbour *et al.*, 2008). Studies have demonstrated that improved glycemic control with intensive insulin therapy in patients with type 1 DM leads to gradual reduction in retinopathy, nephropathy and neuropathy. Individual insulin regiment should be tailored for each person with type 1 DM to enable targeted blood glucose control. With advances in recombinant DNA technology, it is now possible to produce large quantities of insulin with an amino acid structure identical to that of human insulin using strains of genetically altered *Escherichia coli,* bacteria or yeast (Jabbour *et al.,* 2008*).* The main undesirable effect of insulin is that hypoglycemia can cause brain damage, swelling, erythema and stinging occurs especially in the beginning. Insulin allergy to human is unusual but can occur. Some patients develop short lived dependent edema (Patil *et al*., 2011).

In type 1 diabetics, most studies have not found any benefit from exercise because of the likelihood of type 1 diabetics to consume additional carbohydrates in an effort to prevent hypoglycemia which often develops during light to moderate exercise unless the insulin dose is reduced or extra carbohydrate consumed (Bastaki, 2005).

2.6.2 Oral hypoglycemic agents

2.6.2.1 Sulfonylureas

They stimulate insulin secretion from the β-cell. They also appear to sensitize the β-cell to various other insulin secretagogues, such as glucose. An improvement in insulin resistance may also be observed with sulfonylureas. The commonest adverse effects of sulfonylureas are hypoglycemia, which can be severe and prolonged. Allergic skin rashes can occur as well as bone marrow damage although very rare (Patil *et al.*, 2011). Sulfonylureas have a tendency to produce weight gain, although intervention that improves diabetic control in a patient following an isocaloric diet would be expected to result in such an effect (Scobie, 2002).

2.6.2.2 Biguanides

Biguanides lowers plasma glucose levels by enhancing the sensitivity of peripheral tissue to insulin. They do not usually cause hypoglycemia, but accumulates as it is excreted through the renal causing lactic acidosis and therefore it should not be used in patients with renal impairment. It should not also be used in patients with hepatic disease, hypoxic pulmonary disease, heart failure or shock. Vitamin B12 deficiency

may occur due to interference with its absorption when a high dose of metformin is used (Scobie, 2002; Patil *et al.,* 2011). The commonest unwanted side effects of metformin are gastrointestinal disturbances, abdominal pain, and metallic taste (Patil *et al.,* 2011).

2.6.2.3 Alpha-glucosidase inhibitors

They include acarbose and miglitol and are widely used as first line agents in countries like Japan. They slow the absorption of complex carbohydrates from the gastrointestinal tract and are important in controlling post-prandial hyperglycemia, but their blood glucose lowering effect is lower than those of metformin or the sulfonylureas and the side effects of flatulence and bloating limit their tolerability (Scobie, 2002).

2.6.2.4 Meglitinides

They include repaglinide and nateglinide and they act like the sulfonylureas via closure of the K^+-ATP channels in the β-cells, although their receptor binding characteristics are different. They produce a short lived insulin release that is dependent on concentration of glucose. Thus taken before meals, they act to restore the delayed and impaired insulin response to meals seen in type 2 DM, without causing hypoglycemia. Meglitinides may safely be used in combination with biguanides (Scobie, 2002).

2.6.2.5 Thiazolinidiones (Glitazones)

Their exact mode of action is not well understood, but is mediated by activation of the nuclear receptor peroxisome proliferator activated receptor gamma, this leads to

stimulation of insulin sensitive proteins with a reduction of hepatic glucose production and an increase in peripheral glucose uptake. As a monotherapy, these agents are comparable with sulfonylureas and metformin. They reduce intra-abnominal fat deposition but also promote peripheral fat deposition. This latter effect and their tendency to produce edema are associated with weight gain. Thiazolidinediones also causes serious hepatotoxicity effect (Scobie, 2002; Patil *et al.,* 2011).

2.6.3 Exercise

Exercise training raises high density lipoprotein cholesterol, lowers blood pressure, and leads to a 20 to 40% increase in insulin sensitivity by enhancing insulin action in skeletal muscles (Jabbour *et al.,* 2007). All diabetic patients should be encouraged to engage in 30 minutes of modest aerobic exercise 3-4 times per week. The intensity should be gauged to produce an increase in pulse rate to 60-70% of maximum which can be calculated as 220-minus age (Jabbour *et al.,* 2007*).* However exercise may not be ideal for long term care because it is associated with potential risks such as cardiac ischemia, musculoskeletal injuries and hypoglycemia in patients treated with insulin or secretagogues (Fieldman *et al.*, 2009).

2.6.4 Dietary management

In type 1 DM, a diet of low fat, high complex carbohydrates, high fiber and low salt intake is recommended. Total fat intake should not exceed 30% of total energy intake, and less than 10% should come from saturated fats. Complex carbohydrates should comprise more than 50% of the total energy intake. Simple sugars such as sucrose

should only be consumed in moderate amounts, as they do not cause acute hyperglycemia unlike glucose. Dietary fiber should be increased to more than 30g/day, preferably taken in the form of natural soluble fiber as found in legumes, grains, cereals, or fruit. Protein should comprise 10-15% of total energy intake (Scobie, 2002).

There should be calorie restriction and avoidance of sweet foods and drinks for type 2 DM. A long term strategy should be formulated whose goals is to correct obesity, as weight loss will improve blood glucose control, lower blood pressure and lower blood lipid concentrations. A diet of low fat, high complex carbohydrate, high fiber and low calorie intake is recommended. Dietary failure is common in the treatment of obesity associated with type 2 diabetes mellitus; avoidance of fat in the diet should be stressed. An increase in the regular exercise and avoidance of smoking are advisable (Scobie, 2002).

2.6.5 β-cell replacement

There are three general clinical situations that justify this approach. The first is recurrent hypoglycemia with poor symptom recognition despite optimal medical care (Jabbour *et al.,* 2008). The second general indication of β-cell replacement is increase in secondary complications of diabetes for example in patients who have developed kidney failure and are candidates for kidney transplantation. The third indication is psychiatric or emotional disability that prevents patients from cooperating with insulin based therapy (Jabbour *et al.,* 2008).

2.6.6 Mineral elements and antidiabetic activity

Chromium (Cr)

Chromium, in the form of naturally occurring dinicotinic acid -glutathione complex, also known as glucose tolerance factor (GTF), is vital for carbohydrate metabolism as it potentiates the action of insulin. Isolated from brewer's yeast, the active component of GTF was subsequently found to contain trivalent chromium, nicotinic acid, glycine, glutamic acid and cysteine. As such, it normalizes blood sugar levels in subjects with tendencies toward blood sugar fluctuations associated with diabetes (hyperglycemia) and low blood sugar (hypoglycemia) (Anderson, 1980). Chromium increases the number of insulin receptors, enhances receptor binding, and potentiates insulin action (Siddiqui *et al*., 2014).

Selenium (Se)

As with other trace elements, early researchers concentrated on the role of selenium in animal disease conditions. The role of selenium in animal physiology was first established when it was found that it could prevent liver necrosis in vitamin E-deficient rats. Selenium is able to prevent exudative diathesis and pancreatic fibrosis in poultry, hepatosis dietetica in pigs and muscular dystrophy in lambs, calves and other species. It is a vital element for growth and for maintaining optimum fertility status. In humans, selenium increases the growth of fibroblasts in culture. It is also a vital component of an antioxidant enzyme known as glutathione peroxidase. Furthermore, it prevents the occurence of Keshan disease and juvenile cardiomyopathy, found in countries where the soil is low in this essential mineral. An ever increasing number of epidemiological

surveys are linking low dietary selenium with the development of cancer and cardiovascular disorders (Levander *et al.,* 1982)

Zinc (Zn)

The function of zinc in the body metabolism is based on its enzymatic affinity and way of a zinc-enzyme complex or metallo-enzyme. In humans and animals, diabetes causes disturbances in this vital trace element (Kowluru *et al*., 2000). Zinc is required for insulin synthesis and storage and insulin is secreted as zinc crystals. It maintains the structural integrity of insulin (Chausma, 1998). Zinc has an important role in modulating the immune system and its dysfunction in diabetes mellitus may be related in part to the status of zinc (Mocchegianai *et al*., 1989).

Toxic metals like lead (Pb), nickel (Ni), cadmium (Cd) and arsenic (As) deposit in tissues and are non-degradable. Toxic metals react with various proteins in the body that may modify their functions and kinetics. Moreover, when diet is low in essential metals, the body absorbs and makes use of more toxic metals. An abundance of a toxic metal competes with essential metal for enzymes activity and various body physiological functions (Flora, 2009). For example, Zn is required for the activity of many enzymes. In case of Zn deficiency and increased exposure to toxic metals such as lead (Pb), body will use Pb instead of Zn (Duruibe, 2007).

Magnesium (Mg)

Magnesium has an important role in the phosphorylation reactions of glucose and its metabolism. Its deficiency has been implicated in insulin resistance, carbohydrate

intolerance, dyslipidemia and complications of diabetes (Praveena *et al*., 2013). The association between diabetes mellitus and hypomagnesaemia is compelling, because of its wide ranging impact on diabetic control.

Potassium (K)

Normal potassium concentration is necessary for optimal insulin secretion. Deficiency of potassium results more often from excessive losses than from insufficient intakes. Deficiencies arise in abnormal conditions such as diabetic acidosis. Potassium depletion can result in reduced glucose tolerance. Sodium and potassium ions play an important role in the disease related disorder (Rajendra *et al.,* 2007). Lower levels of potassium have been found to be associated with a higher risk of diabetes in some studies (Ranee *et al*., 2012).The results of this experiment (Hales and Milner, 1967) showed that a rise in the potassium concentration of the incubation medium caused a reversible stimulation of insulin secretion.

Vanadium (V)

Numerous investigations have demonstrated the beneficial effect of vanadium salts on diabetes in diabetic rats, in rodents with genetically determined diabetes and in human subjects. In 1980 vanadium was reported to mimic the metabolic effects of insulin in rat adipocytes. Vanadium therapy was shown to normalize blood glucose levels in diabetic induced rats and to cure many hyperglycemia related deficiencies (Rajendra *et al.,* 2007).

Iron (Fe)

Iron has several vital functions in the body which are involved in oxidation- reduction reactions, Heamoglobin oxygen transport and also a cofactor for numerous other enzymes (Rajendra *et al.*, 2007).

Manganese (Mn)

Manganese functions as a key constituent of metallo-enzymes activator. In experimental animals, pancreatectomy and diabetes have been correlated with decreased manganese levels in blood. Manganese supplements have reversed the impaired glucose utilization induced by manganese deficiency in guinea pigs. Manganese may act like insulin in increasing the transport of glucose into adipose tissue by enhancing an existing low level of insulin. Manganese requirements are low, and many plant foods contain significant amounts of this trace mineral (Rajendra *et al.*, 2007).

Copper (Cu)

The primary function of copper in the body is to serve as constituents of many biologically important enzymes. Thus enzymes which contain copper in the active site catalyze the oxidation of ferrous iron to ferric iron. Copper is required for absorption and transport of iron and it plays a key role in heamoglobin synthesis. High plasma copper concentrations are found in people with diabetes mellitus (Rajendra *et al.*, 2007).

2.6.7 Diabetes and plant phytochemicals

Plant-based medicinal products have been known to man since ancient times, (Subbulakshmi and Naik, 2001). Plants have been the primary source of drugs and many of the currently available drugs have been directly or indirectly derived from plants. For example, the popular hypoglycemic drug glucophage (metformin) is derived from *Galega officinalis* (Grover *et al*., 2002). About 800 plant species have been reported to possess antidiabetic properties (Alarcon-Aguilara *et al*., 1998).

Several species of medicinal plants used in traditional treatment and management of diabetes worldwide have been evaluated (Brai *et al.,* 2007; Gondwe *et al.,* 2008). Generally, plants rich in alkaloids and flavonoids have been observed to possess hypoglycemic properties. In south west of Nigeria, coconut water extract of *Parinari polyandra benth* seeds is used in the treatment of diabetes and acclaimed to have strong anti-diabetic effect (Ighodaro *et al.* 2012).

Alkaloids: The major alkaloid component that is known to suppress hyperglycemia is alkaloid I-ephedrine. It has demonstrated promotion and regeneration of pancreatic islets cells following atrophy, restores insulin secretion, and thus reduces hyperglycemia (Elliot *et al*., 2000). Hydrolysis of Alkaloids like pyrrolizidine alkaloids (PAS) via N-oxidation and demethylation in the liver leads to intense cellular alterations known as megalocytosis. Alkaloids lead to fatty degeneration, proliferation of the biliary tract epithelium, megalocytosis, liver cirrhosis, nodular hyperplasia and adenomas or carcinomas (Zeinsteger *et al*., 2008).

Flavonoids: Flavonoid glycosides are constituents that have been used in clinical treatment of diabetes to improve sensitivity of insulin and include strictinin, isostrictinin and pedunculagin (Zhou, 2009). Flavonoids can be widely classified into different categories like flavonols, catechins and flavones. Quercetin is an important flavanoid known to possess a vast array of pharmacological activities (Mukherjee, 2006). The administration of quercetin intraperitoneally to normal as well as streptozocin induced diabetic rats resulted in marked reduction in plasma glucose level of diabetic animals while the glucose level of the normoglycemic rats remained unaltered. Quercetin also suppressed the glucose level in diabetic rats in a glucose tolerance tests, reduced plasma cholesterol and triglycerides significantly and increased their hepatic glucokinase activity probably by enhancing the insulin release from pancreatic islets of the diabetic rats (Vessal, 2003).

Some flavanoids such as kakonein, flavone C-glycoside and caesalpin P have antidiabetic activity (Li *et al*., 1999) and most of them have improved functions of pancreatic islet cells. The polyhydroxylated flavonol myricetin demonstrated insulinomimetic properties stimulating lipogenesis and glucose transport in the adipocytes. This compound has no effect on insulin receptor, autophosphorylation or glucose uptake (Elliot *et al*., 2000).

Saponins are glycosides of triterpenes and steroids and commonly occur in higher plants. The sugars found in saponins are hexoses, 6-deoxyhexoses, pentoses, uronic acids, or amino sugars (Yang, 2009). Examples of saponins include triterpenoids and

steroidal glycosides, they are found naturally in many plants and are known to be possessing potent hypoglycemic activity (Mukherjee, 2006). These saponins directly and/or indirectly regulate the activity of enzymes related to glucose metabolism. Saponins are poorly absorbed in the gastrointestinal tract and its overdose induces bloody diarrhea. Saponins are strong laxatives and in the small intestines, toxic doses lead to acute erosion of the superficial or middle parts of the intestinal villi resulting in hemorrhage inside the lamina propia (Yang, 2009). It also causes hemorrhage in many liver lobules and congestion of central veins and liver sinusoids. In the kidneys, saponins results in hemorrhage in the glomeruli and focal destruction of the renal tubules. The toxic level of saponins therefore, causes cardiac failure, acute hypoglycemia and hepatorenal damage leading to sudden death (Diwan, 2006).

Steroids are some of the familiar compounds occurring naturally in plants and animals, possessing a nucleus of cyclopentanohydrophenanthrene and include sterols, bile acid, steroid hormones, cardiac glycosides, and toad poison. Steroidal saponins form part of important steroids (Yang, 2009).

Tannins are polyphenols that are obtained from various parts of different plants belonging to multiple species. They are found in abundance in the tree bark, wood, fruit, roots, fruit pod, leaves, and also in plant gall. Tannins can be classified into two broad groups, hydrolysable tannins and condensed tannins. Clinically all the forms of tannins may participate in managing glucose level in blood (Kumari, 2014a).

2.6.8 Remedies of plant origin

In the North Rift Valley region of Kenya, along the Kerio valley, some indigenous trees are gaining popularity as alternative medicine in the management of diabetes mellitus. These plants are *Maerua subcordata (Gilg) Dewolf, Chasmanthera dependens (Hochst), Pappea capensis, Syzigium cordatum and Mayrtenus undata. Chasmanthera dependens* (Hochst), commonly called *Chasmanthera*, is a medicinal plant used for the treatment of several disease that include red-eye infections, venereal diseases and management of fractures and as a general tonic for physical and nervous debilities. The methanolic extract of the dried leaves has also been reported to have anti-inflammatory and analgesic effects on laboratory animals while the aqueous and ethanolic crude extracts of the leaves have been reported to have antifungal activity (Ogunlesis *et al*., 2008).

Capparaceae Maerua subcordata is a shrub found in arid or semi arid rocky and sandy forests. The deep rooted tubers have been used traditionally to manage Diabetes mellitus as well as a water purification agent (Mavura *et al*., 2008).

Mayrtenus species are either trees or shrubs growing to a height of one to nine meters. It is widely used in folk medicine as antitumor, anti asthmatic and anti-ulcer agents and as treatments for stomach problems, as analgesics, anti-inflammatory and antimicrobials. Previous studies of the plant isolated 12-oleanene and 3, 4-seco-12 oleanene triterpene acids that had antibacterial activity against *staphylococcus aureus* and *pseudomonas aerugenosa* and promising antifungal activity against *Cryptococcus neoformans* (Muhammed *et al*., 2000).

Syzigium cordatum is a medium-sized tree, 6-15 (max. 20) m in height; dwarf forms 30-45 cm high have been reported; young trunks banded and blotched in grey and white and are fairly smooth; in old trees the bark is dark brown, light grey or reddish, thick, rough, fissured and can be pulled off in thick, corklike, square pieces; young stems squarish with winged edges. It hybridizes freely with *S. guineense* and *S. gerrardii* where they occur together. Flowers bloom from spring to winter and are popular with bees and other insects, which are the pollinating agents. The fruits are eaten by numerous animal species that act as the dispersal agents for the seeds. It occurs in lowlands as well as medium- to high latitude forests, along stream banks and in riverine thickets. *Syzigium* products are used as food (fruits), as fodder, apiculture, fuel, timber, tannin and as fish poison. The medicinal value includes boiled roots and bark decoction as remedy for indigestion and gidding while extract of the leaves is used as a purgative and diarrhea treatment (Orwa *et al., 2009*).

Pappea capensis (Litchi.) tree belongs to the Litchi family *Sapindaceae*. The tree grows up to 3.9 m tall and can be deciduous or evergreen depending upon the prevailing environmental conditions (Van and Gericke, 2000; Mng'omba *et a*l., 2007; 2008). It produces fleshy leaves which can be processed into vinegar, jelly and jam (Palmer and Pitman, 1972). Seeds are rich in edible, non-drying and fairly viscous oil which constitutes about 74% and is used for making soap and oiling guns (van and Gericke, 2000). This plant is fairly adapted to a wide range of ecological areas and it is known to be drought-tolerant thus able to grow in marginal lands. In Kenya, it is distributed in Lukenya hills, Ngong hills, and northern Kapenguria, semi-arid regions of southern part

of Embu County such as Siakago and in Keiyo south in Elgeiyo –Marakwet County. It is a good fodder for livestock and produces edible fruits. Among Kenyan communities, the boiled stem barks are used traditionally to treat whooping cough and sparingly the leaves are used in the management of diabetes mellitus (Karau *et al.*, 2012).

CHAPTER THREE

MATERIALS AND METHODS

3.1 Study site

The study was done at the Department of Biochemistry, Microbiology and Biotechnology, School of Pure and Applied Science, Kenyatta University, Kenya.

3.2 Collection and preparation of plant materials

Plant parts were collected from Songita village, Kiptuilong location, Keiyo South Constituency in Elgeiyo Marakwet County. They were authenticated by a taxonomist at the Kenya National Museum and voucher specimens deposited in their herbarium for future reference. They were then dried in a cool dry place for four weeks after removal of the outer cover of the bark and splitting into small pieces before grinding into powder using an electric grinder. The powder was kept in a cool dry place at room temperature in dry plastic bags ready for extraction.

3.3 Extraction of plant material

Approximately one hundred grams (100g) of the powder was extracted in one liter of distilled water at 60^0C in a shaker for 6hrs and thereafter left to cool to room temperature. The extracts were filtered into clean dry conical flasks through gauze then through Whatman filter paper No 1 under vacuum pressure. Filtration was repeated until the supernatant collected in each case was clear. The filtrate was then freeze dried in 200ml portions using Freeze Dryer for 48hrs then stored in air tight containers at -20^0C ready for bioassay.

3.4 Preparation of plant extracts for injection into mice

The freeze dried plant extracts were dissolved in 1ml physiological saline to make five doses for either oral or intraperitoneal administration to mice. The following dose preparations were made: 5.75, 11.13, 21.51, 41.61 and 80.5 mg were dissolved in 1 ml of physiological saline. 0.1 ml of each drug preparation was either orally or intraperitoneally administered to each mouse of average weight 23g in a group of five for each dose to give a final concentration of 25, 48.4, 93.5, 180.9 and 350 mg/kg body weight. Insulin dose was prepared by dissolving 0.23 international units of insulin in 1 ml physiological saline to intraperitoneally administer 0.1ml to each mouse in a group of five to give a final dose of 1 IU/kg body weight. Similarly, 4.6mg of Glibenclamide was dissolved in 1ml of physiological saline to administer orally 0.1 ml to each mouse in a group of five to give a final dose of 20 mg/kg body weight. The five mice in each of the normal control mice and alloxan induced diabetic mice were either orally or intraperitoneally administered with 0.1 ml of physiological saline each (Njeri *et al*., 2017).

3.5 Experimental design

This was a completely randomized experimental design. Swiss albino male mice of 4-6 weeks old and weighing between 21-25g (average weight 23 g) were used for the study. The animals were bred in the Department of Biochemistry, Microbiology and Biotechnology, Kenyatta University animal house and were fed on a standard pellet diet and water. They were randomly grouped into eight groups of five mice each 3 days before the start of the experiment. Group I consisted of normal control mice orally or

intraperitoneally administered with 0.1 ml physiological saline. Group II consisted of alloxan induced diabetic mice either orally or intraperitoneally administered with 0.1 ml physiological saline. Group III consisted of alloxan induced diabetic mice either orally administered with 0.1 ml of Glibenclamide (0.46 mg/ml of physiological saline) to give a final dose of 20 mg/kg body weight or intraperitoneally administered with 0.1 ml of insulin (0.23 IU/ml of physiological saline) to give a final dose of 1IU/kg body weight. Groups IV, V, VI, VII and VIII consisted of alloxan induced diabetic mice either orally or intraperitoneally administered with 0.1 ml of each of five aqueous plants extracts to give a final dose of 25 (5.75 mg/ml physiological saline), 48.4 (11.13 mg/ml physiological saline), 93.5 (21.51 mg/ml physiological saline), 180.6 (41.61 mg/ml physiological saline) and 350 (80.5 mg/ml physiological saline) mg/kg body weight. Blood glucose levels were estimated using a glucometer and mice with a value above 10.0 mmol/L was considered diabetic and was therefore included in the *in vivo* antidiabetic experimental study.

3.6 Collection of blood samples and glucose determination

Blood was obtained from the tails of the mice by snipping the tips with sterile scissors after swabbing with 70% ethanol. Bleeding was enhanced by gently milking the tail from the body towards the tip and a drop of blood was placed onto a glucose strip and glucose level measured using SoftStyle glucometer from Chem-Labs Limited in mmol/L.

3.7 *In vivo* hypoglycemic activity assay

Preliminary blood glucose level was determined for all animal groups before treatment with either normal saline, insulin, glibenclamide or plant extracts. Hypoglycemic activity after treatment was analyzed by collecting blood at 0, 2, 4, 6, 8 and 24 hours for post treatment glucose determination and results recorded upon every collection. During the experiment, the animals were allowed free access to water and food.

3.8 Phytochemical analysis of plant extracts

The alkaloids, flavonoids, tannins, saponins and total phenols in the five aqueous plants extracts were quantitatively estimated using standard methods as described by Piero *et al.*, (2012).

3.8.1 Quantitative Determination of Saponins

One gram (1.0 g) of each of the five aqueous plants extracts samples was extracted with methanol in a Soxhlet apparatus for 8 hours according to Obadoni and Ochuko, (2001). The methanolic extracts were evaporated under reduced pressure to afford crude methanolic extract which were partitioned between hexane and water in separating funnels. The aqueous layers were then extracted with diethyl ether. The aqueous layers were recovered while the diethyl ether layers were discarded and purification process repeated. The aqueous layers were further partitioned with *n*-butanol three times in each case. The combined butanol extracts were washed twice with 15 ml of 5 % sodium chloride and then evaporated to dryness in *vacuo* to yield crude saponins whose weights

were recorded and then expressed as percentage of the original weight of the aqueous extract.

3.8.2 Determination of Alkaloids

The alkaloid content was determined gravimetrically using a method used by Harborne, (1998) with some modifications where 1.0 g of each of the five aqueous plants extracts sample was first defatted three times using hexane followed by extraction using 50 ml of 10 % acetic acid in ethanol. The mixture was shaken well, covered and allowed to stand for 4 hours. The mixtures were then filtered and the extracts concentrated in water bath at 70^{O}C (Julabo, USA) until 0.50 ml of the original volume was attained. Concentrated ammonium hydroxide was then added drop wise in order to precipitate the alkaloids.

Pre-weighed Whatman filter papers were used to filter off the precipitates which were then washed with 1% ammonium hydroxide solution. The filter papers containing the precipitates were dried in a hot air oven (KOMEG, China) at 60^{o}C for 30 minutes, transferred into a desiccator (Boekel scientific) to cool and then reweighed until constant weights were obtained. The weights of the alkaloid were determined by weight differences of the filter papers with and without precipitate. The experiments were replicated twice for each sample and the readings recorded as an average of the two replicates.

3.8.1.3 Determination of flavonoids

The total flavonoid concentration was measured by the aluminum chloride colorimetric assay according to Marinova *et al*., (2005). 0.15 g of each of the five aqueous plants extracts was added to 4 ml of double distilled water in a 10 ml volumetric flask. To the above mixture, 0.3 ml of 5 % $NaNO_2$ was added. After 5 minutes, 0.3 ml of 10 % $AlCl_3$ was added. After 6 min, 2 ml of 1M NaOH was added and the total volume was made up to 10 ml with double distilled water. The solution was mixed well and the absorbance was measured at 510 nm against a blank. The flavonoid content was determined using quercetin as standard.

3.8.1.4 Determination of Tannins

The tannins were determined as follows: 2 g of each of the five aqueous plants extracts were extracted three times in 3ml of 70 % acetone. After centrifuging, the sample supernatant was removed. Different aliquots were taken and final volume adjusted to 3 ml with distilled water. The solution after vortexing was mixed with 1 ml of 0.016M $K_3Fe(CN)_6$, followed by 1 ml of 0.02M $FeCl_3$ in 0.1M HCL. Vortexing was repeated and the tubes were kept as such for 15 minutes. An aliquot of 5 ml stabilizer (3:1:1 ratio of water, H_3PO_4 and 1 % gum Arabic) was added followed by revortexing. Absorbance was measured at 700 nm against the blank. A standard curve was plotted using various concentrations of 0.001M garlic acid (Gurib-Fakim, 2006).

3.8.1.5 Estimation of phenols

The total phenolic content was determined using Folin-Ciocalteau reagent and garlic acid as the standard according to the method by Rasineni *et al*., (2008). 500 mg of plant extracts was weighed and homogenized in 10 ml of aqueous acetone (70 %). The homogenates was centrifuged at 10000 x g for 20 minutes and the supernatants used in determination of phenol as follows: 0.5 ml of Folin-Ciocalteau 2N reagent was added to 2.5 ml of the supernatant and then 2 ml of 10 % sodium carbonate in ethanol. The mixture was incubated for 5 minutes at 20^{o}C and the absorbance read in triplicates at a wavelength of 710 nm.

3.8.2 Estimation of phytonutrients

The different trace elements present in the plant extracts were determined using Energy Dispersive X-ray Fluorescence (EDXRF) analytical technique and Atomic Absorption Spectrophotometer (AAS).

3.8.2.1 Elemental analysis by Total Reflection X-Ray Fluorescence (TXRF) system

TXRF system was used to determine the content of sodium (Na), magnesium (Mg), potassium (K), calcium (Ca), titanium (Ti), vanadium (V), manganese (Mn), iron (Fe), copper (Cu), zinc (Zn), gallium (Ga), arsenic (As), selenium (Se), bromine (Br), rubidium (Rb), strontium (Sr), nickel (Ni), lead (Pb), and uranium (U) in the lyophilized aqueous plants extracts samples as described by Hagen, (2007).

3.8.2.2 Sample preparation

Samples were prepared by weighing three sets of 1 g each of the lyophilized aqueous plants extracts samples into clean vials and dissolved in 10 ml of double distilled water before the addition of 20 µL of 1000ppm gallium stock solution into each sample (as internal standard) resulting into a concentration of 2ppm Ga in each sample. Each sample was homogenized for 1 minute using a vortex mixer. Aliquots of 10 µL of each sample were pipetted out using a micropipette onto a clean quartz carrier. The carriers were then dried in an oven to evaporate the liquid.

3.8.2.3 TXRF system

The main principle of X-ray Fluorescence Spectroscopy (XRF) is that when atoms are irradiated with X-rays, they emit secondary X-rays called fluorescence radiation. These fluorescence radiations are characteristic for a particular atom (element) and are of specific energy which makes it possible for qualitative and quantitative analyses.

3.8.2.4 Sample spectrum acquisition and quantitative analysis

Each sample carrier was irradiated for 1000 seconds using an S2 PICOFOX TXRF Spectrometer which was operated at 50 kV and a current of 1000 µA. The spectrophotometer uses a molybdenum anode. Evaluation of the measured spectra was done using S2 PICOFOX software on the basis of the chosen elements. Using the same software (S2 PICOFOX), concentrations were calculated based on the net intensities of the element peaks as per the following formula:

$$Cx = \frac{Nx / Sx}{Nis / Sis} xCis$$

Where,

Cx Concentration of the analyte

Cis Concentration of the internal standard

Nx Net intensity of the analyte

Nis Net intensity of the internal standard

Sx Relative sensitivity of analyte

Sis Relative sensitivity of internal standard

3.8.2.5 Atomic Absorption Spectrophotometry (AAS)

This technique was used for the analysis of magnesium, chromium and cadmium. Samples and standard solutions were prepared as described by Piero *et al.*, (2012) with slight modifications. Suitable amounts of standard stock solutions of each element were taken in a series of 100 ml volumetric flasks. The solutions were diluted to volume using distilled-deionized water, mixed thoroughly and transferred into plastic beakers. Working standard solutions for each element were prepared within a given range (1ppm, 5ppm, 10ppm, 15ppm, 20ppm, and 25ppm). Standard blank reagents for each element were prepared by adding all the reagents, except the target element being determined. No sample digestion was required as the freeze dried aqueous extracts of the plant samples were used.

After setting the AAS instrument to the right wavelengths and temperatures for each element, the respective standard and sample solutions were aspirated into the flame in turns to determine their respective absorbance. Distilled-deionized water was always flushed into the flame to re-establish the zero absorbance. The procedure was repeated twice for each sample and element. The mean absorbance for each sample solution and standard solutions were calculated and recorded. Calibration curve for each element was prepared by plotting a graph of mean absorbance against corresponding concentrations of the standard solutions. Microsoft Excel computer software was used to convert absorbance readings to concentrations of elements in each sample analyzed with better accuracy than the manual graphical method. The program gave concentrations of the diluted and undiluted samples directly. Concentration values obtained for the diluted samples were corrected by multiplying with the respective dilution factors and final values expressed as mg/g.

3.9 Preliminary *in vivo* toxicity evaluation

The mice were divided into three groups each of five mice .Group I served as the untreated normal control and were administered with 0.1 ml of physiological saline. Group II and Group III mice were treated with 1g/kg body weight of the plant extracts orally and intraperitoneally respectively, daily for 28 days. During the period, mice were allowed free access to mice pellets and water and were observed for any signs of general illness and change in behavior. Mice were sacrificed on the 28th day. The body weight of each mouse was assessed during acclimatization period before commencement of dosing, once weekly during dosing period and on the day of

sacrifice. On sacrificing the mice, the heart, brain, liver, lung, spleen, kidney and testis were carefully dissected out and their weights recorded. Sample pieces of each organ were collected and stored in 10% formalin. Blood was also drawn from the heart of each sacrificed mice and divided into two different containers for determination of hematological and biochemical parameters.

3.10 Hematology

Blood samples collected in EDTA were analyzed for white blood cells, red blood cells, hemoglobin, packed cell volume, mean cell hemoglobin, mean cell volume platelets and differential count using a Coulter Counter.

3.11 Biochemical assays

Blood samples collected in plain vaccutainer were allowed to stand for three hours for complete clotting and centrifuged at 3000 rpm for 5 minutes. The clear serum was aspirated off and stored at -20^{o}C until required for biochemical analysis. Determination of biochemical parameters was done in the Department of Laboratory Medicine, Kenyatta National Hospital. The biochemical parameters determined on the sera specimen using the Olympus 640 Chemistry Auto-Analyzer were Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Lactate dehydrogenase (LDH), α-Amylase **(**α-AMYL), Total bilirubin (T-BIL), Direct bilirubin (D-BIL), Urea, Creatinine (CREAT), Total Cholesterol (T-CHOL), High density lipoprotein (HDL-C), Low density lipoproteins (LDL-C) and Triacylglycerols (TG). All reagents for the

machine were commercially prepared to fit the required volumes and concentrations. The reagents were in specific containers referred to as reagent cartridges.

The reagent cartridges were bar coded for the identification by the machine. The machine was programmed for the selected tests for each sample. The sample holders were then placed into the autoloader assembly. A number of events that occurred simultaneously were performed automatically under the direct control of the instrument microprocessor. All the assays were performed based on the standard operating procedures (SOPs) written and maintained in the Department of Laboratory Medicine, Kenyatta National Hospital.

3.11.1 Determination of serum levels of Aspartate aminotransferase (AST)

The serum aspartate aminotransferase level was determined by the method described by Henry *et al.,* (1960). AST reagent was used to measure AST levels by an enzymatic method. In the reaction, AST catalyzes the reversible transamination of L-aspartate and α-ketoglutarate to oxaloacetate and L-glutamate. The oxaloacetate is then reduced to malate in the presence of malate dehydrogenase (MDH) with concurrent oxidation of reduced β-nicotinamide adenine dinucleotide (NAD). The ratio of the sample to reagent was 1 part sample to 11 parts reagents (23μL: 253μL reagent). The absorbency was measured at 340 nm and its change was directly proportional to the levels of AST. The machine calculated and expressed the level in IU/L. The reaction took place at 37^0C for three minutes. The principle of the reaction is as follows:

α-ketoglutarate + L-aspartate $\xrightarrow{AST}$ L-glutamate + Oxaloacetate

Oxaloacetate + NADH + H^+ $\xrightarrow{MDH}$ Malate + NAD^+

3.11.2 Determination of serum levels of Alanine aminotransferase (ALT)

The method used to determine serum alanine aminotransferase was described by Henry *et al.,* (1960). The ALT reagent was used to measure ALT level by an enzymatic rate method. In the reaction, the ALT catalyzes the reversible transamination of L-alanine and α-ketoglutarate to pyruvate and L-glutamate. The pyruvate is then reduced to lactate in the presence of Lactate dehydrogenase (LDH) with concurrent oxidation of β-Nicotinamide Adenine Dinucleotide (reduced form) (NADH) to β-Nicotinamide Adenine Dinucleotide (oxidized form) (NAD^+).

Pyridoxal-5-phosphate was required in this reaction as a cofactor for the transaminase activity by binding to the enzyme using Schiff-base linkage. The ratio of the sample to reagent was 1 part sample to 11 parts reagents (23 μL: 253μL reagent). The absorbance was measured at 340 nm and its change was directly proportional to the level of ALT. The machine calculated and expressed the level in IU/L. The reaction took place at 37^0C for 3min. The principle of the reaction is as follows:

α-Ketoglutarate + L-alanine $\xrightarrow{ALT}$ L-Glutamate + Pyruvate

Pyruvate + NADH + H^+ $\xrightarrow{LDH}$ Lactate + NAD^+

3.11.3 Determination of serum levels of alkaline phosphatase (ALP)

The ALP reagent was used to measure ALP level by kinetic method using a 2-amino-2-methyl-1-propanol (AMP) buffer (International Federation of Clinical Chemistry, 1983). In the reaction, ALP catalyzed the hydrolysis of the colorless organic phosphate ester substrate (p-nitrophenylphosphate) to the yellow colored product (p-nitrophenol and phosphate). This reaction occurred at alkaline pH of 10.3. The ratio of the sample to reagent was 1 part sample to 50 parts reagents (5µL: 250µL reagent). The absorbance was measured at 410 nm and this change was directly proportional to the level of ALP. The machine calculated and expressed the level in IU/L. The reaction took place at 37^0C for three minutes. The principle of the reaction is as follows:

$$\text{4-NPP} + H_2O \xrightarrow{ALP} \text{4-NPO}$$

3.11.4 Determination of serum levels of γ-glutamyltransferase (γ-GT)

GGT reagent was used to measure γ-glutamyltransferase level by an enzymatic kinetic UV rate method. In the reaction, γ-glutamyltransferase catalyzes the transfer of the glutamyl group from the substrate to glycylglycine forming glutamylglycylglycine and 5-amino-2-nitrobenzoate. A volume of 5 µL of the sample was reacted with 200 µL of the reagent. The rate of formation of 5-amino-2-nitrobenzoate was proportional to the level of GGT present in the sample and was measured kinetically at 405nm. The level was calculated and expressed in U/L. The reaction took place at 37^oC for three minutes. The principle of the reaction is as follows:

$$\text{L-γ-glutamyl-3-carboxy-4-nitroanilide} + \text{glycylglycine} \xrightarrow{GGT} \text{L-γ-glutamylglycylglycine} + \text{5-amino-2-nitrobenzoate}$$

3.11.5 Determination of serum levels of lactate dehydrogenase (LDH)

This was an enzymatic kinetic UV test for the quantitative determination of LDH. In the reaction, LDH catalyzes the oxidation of lactate to pyruvate coupled with the reduction of NAD^+ to NADH. A 2 µL aliquot of sample was reacted with 40 µL of reagent and the change in absorbance due to reduction of NAD was monitored at 340nm. This change was directly proportional to the concentration of LDH in the sample and was used to calculate and express concentration in U/L. The reaction took place at 37^{o}C for three and half minutes. The pH optimum for lactate to pyruvate reaction is 8.8 to 9.8. The principle of the reaction is as follows:

$$\text{Lactate} + NAD^+ \xrightarrow{LDH} \text{Pyruvate} + NADH + H$$

3.11.6 Determination of serum levels of α-amylase (α-AMYL)

Amylase reagent was used to measure the concentration of amylase by a kinetic color method using Olympus Auto analyzer. In the reaction, 2-chloro-4-nitrophenyl-α-D-maltotrioside ($CNPG_3$) substrate reacted with amylase in the serum to release 2-chloro-4-nitrophenol (CNP) from the substrate which was directly proportional to the concentration of amylase in the sample. A 3 µL sample was reacted with 300 µL of reagent and the change in absorbance was monitored at 340nm, due to reduction of NAD. This change was directly proportional to the concentration of α AMYL in the sample and was used to calculate and express concentration in U/L. The reaction took place at 37^{o}C for three and half minutes. The principle of the reaction is as follows:

$$CNPG_3 + H_2O \xrightarrow{Amylase} \text{CNP} + \text{Maltotriose}$$

3.11.7 Determination of serum levels of total bilirubin (T-BIL)

Total bilirubin reagent was used to measure BIL-T concentration by timed end point reaction. In the presence of hydrochloric acid (HCL), T-BIL was coupled with diazotized Sulfanilic acid (pH 1.4) forming azobilirubin. The chemistry analyzer automatically aliquoted 9 µL sample and 120 µL BIL-T reagents then photometrically measured azobilirubin whose color intensity was directly proportional to the T-BIL concentration. The absorbance was measured at 552 nm for two minutes at 37^0C. The analyzer automatically calculated the T-BIL concentration using a factor and expressed it in µmol/L. The principle of the reaction is as follows:

Sulfanilic acid + $NaNO_2$ $\xrightarrow{HCL}$ Diazotized Sulfanilic acid

Bilirubin + Diazotized Sulfanilic acid $\xrightarrow{pH1.4}$ Azobilirubin

3.11.8 Determination of serum levels of direct bilirubin (D-BIL)

Direct bilirubin reagent was used to measure D-BIL concentration by timed end point reaction. In the presence of hydrochloric acid (HCl), D-BIL was coupled with diazotized Sulfanilic acid (pH 1.4) forming azobilirubin. The chemistry analyzer automatically aliquoted 9 µL sample and 120 µL D-BIL reagent then photometrically measured azobilirubin whose colour intensity was directly proportional to the D-BIL concentration. The absorbance was measured at 552 nm for two minutes at 37^OC. The analyzer automatically calculated the D-BIL concentration and expressed it in µmol/L. The principle of the reaction is as follows:

Sulfanilic acid + $NaNO_2$ $\xrightarrow{HCL}$ Diazotized Sulfanilic acid

Bilirubin + Diazotized Sulfanilic $\xrightarrow{pH1.4}$ acid Azobilirubin

3.11.9 Determination of serum levels of urea

The method used is described by Tiffany *et al.*, (1972). The BUN reagent was used to measure the concentration of urea by an enzymatic rate method. In the reaction, urea was hydrolyzed by urease to ammonia and carbon dioxide. Glutamate dehydrogenase (GLDH) catalyzes the condensation of ammonia and α-ketoglutarate to glutamate with concomitant oxidation of reduced β-Nicotinamide Adenine Dinucleotide (NADH) to β-Nicotinamide Adenine Dinucleotide (NAD^+). The ratio of the sample to reagent was 1 part sample to 100 parts reagents (3μL: 300μL reagent). The absorbance was measured at 340 nm and this change was directly proportional to the concentration urea. The machine calculated and expressed the concentration in μM. The reaction took place at 37^0C for one minute. The principle of the reaction is as follows:

$$\text{Urea} + H_2O \xrightarrow{Urease} 2NH_3 + CO_2$$

$$NH_3 + \alpha\text{-Ketoglutarate} + \text{NADH} \xrightarrow{GlDH} \text{L-Glutamate} + NAD^+$$

3.11.10 Determination of serum levels of Creatinine (CREAT)

Creatinine reagent was used to measure CREAT concentration by modified Jaffe reaction method. In the reaction, Creatinine reacts with picric acid in alkaline solution to form Creatinine-picric acid complex. The analyzer automatically proportioned 15 μL sample and 250 μL Creatinine reagent into the reaction cuvette. The rate of color formation was monitored and increase in absorbance determined at 512 nm for two minutes at 37^0C. The analyzer automatically calculated the CREAT concentration and expressed it in mmol/L. The principle of the reaction is as follows:

Creatinine + Picric acid $\xrightarrow{pH13}$ Creatinine-picric acid (yellow-red) complex

3.11.11 Determination of Total Cholesterol (T-CHOL)

Cholesterol esters in the sample were hydrolyzed in the presence of cholesterol esterase to form cholesterol and fatty acids. The cholesterol was then oxidized in the presence of cholesterol oxidase to cholestene-3-one and hydrogen peroxide. Hydrogen peroxide formed reacted with 4-aminoantipyrine and phenol in the presence of peroxidase to form a red dye quinoneimine and water. 2.5 µL of sample was reacted with 250 µL of reagent and the change in absorbance was monitored at 540 nm. This change was directly proportional to the concentration of T-CHOL in the sample and was used to calculate and express concentration in mmol/L. The reaction took place at 37°C for two minutes. The principle of the reaction is as follows:

Cholesterol esters $+H_2O \xrightarrow{CHE}$ Cholesterol + Fatty acids

Cholesterol + $O_2 \xrightarrow{CHOD}$ 4-cholestenone + H_2O_2

$2H_2O_2$ + 4-AP + Phenol $\xrightarrow{POD}$ Quinoneimine + $4H_2O$

3.11.12 Determination of serum triacylglycerols (TG)

Enzymatic-colorimetric determination of triacylglycerols was done according to Tietz *et al*., (1995). This was based on a series of coupled enzymatic reactions. Triacylglycerol in the sample was hydrolyzed by lipase to give glycerol and fatty acids. The glycerol was phosphorylated by ATP in the presence of glycerol kinase (GK) and Mg^{2+} to produce glycerol-3-phosphate. Glycerol-3-phosphate was oxidized in the presence of glycerol phosphate oxidase (GPO) to produce hydrogen peroxide (H_2O_2) and

dihydroxyacetone phosphate. The hydrogen peroxide formed reacts with 4-aminoantipyrine (4-AAP) (aminophenazone) and 3, 5-dichloro-2-hydroxybenzesulfonic acid (DHBS) in the presence of peroxidase to form a red quinoneimine dye. 2 µL of sample was reacted with 200 µL of reagent and the change in absorbance was monitored at 660 nm. This change was directly proportional to the concentration of TG in the sample and was used to calculate and express concentration in mmol/L. The reaction took place at 37°C for two minutes. The principle of the reaction is as follows:

Triacylglycerols $+H_2O \xrightarrow{LPL}$ Glycerol + Fatty acids

Glycerol +ATP $\xrightarrow{GK}$ Glycerol-3-phosphate + ADP

Glycerol-3-Pi + $O_2 \xrightarrow{GPO}$ Dihydroxyacetone-Pi + H_2O_2

H_2O_2 +4-AP + ρ-Chlorophenol $\xrightarrow{POD}$ Quinoneimine + H_2O

3.11.13 Determination of serum high density lipoproteins cholesterol (HDL-C)

Antihuman β-lipoprotein antibody binds to β-lipoproteins other than HDL-C (LDL-C, VLDL-C and chylomicrons). The antigen antibody complexes formed block enzyme reactions. HDLC was quantified by the presence of an enzyme chromogen system. 2.5 µL of sample was reacted with 250 µL of reagent and the change in absorbance was monitored at 540 nm. This change was directly proportional to the concentration of HDL in the sample and was used to calculate and express concentration in mmol/L. The reaction took place at 37°C for two minutes. The principle of the reaction is as follows:

LDL, VLDL and chylomicrons $\xrightarrow{Antihuman\ \beta-lipoprotein\ antibody}$ Antibody-antigen complexes

HDL-C + H_2O + $O_2 \xrightarrow{CHO+CHE}$ Cholestene-3-one + Fatty acid + H_2O_2

$2H_2O_2$ + 4-AAP + Phenol $\xrightarrow{POD}$ Quinoneimine (red) dye + $4H_2O$

3.11.14 Estimation of LDL-Cholesterol (LDL-C)

A protecting agent protected LDLC from enzymatic reactions. All non-LDL-C lipoproteins (HDL-C, VLDL-C, chylomicrons) were broken down by reaction with cholesterol esterase (CHE) and cholesterol oxidase (CHO). H_2O_2 produced by this reaction was decomposed by catalase in the first step of the reaction. In the second step of the reaction, the protecting agent was released from the LDL-C and the catalase inactivated by sodium azide. LDL-C was quantified by the CHO/POD system. 2.5 µL of sample was reacted with 250 µL of reagent and the change in absorbance was monitored at 540 nm. This change was directly proportional to the concentration of LDL-C in the sample and was used to calculate and express concentration in mmol/L. The reaction took place at 37°C for two minutes. The principle of the reaction is as follows:

LDL-C + H_2O + O_2 $\xrightarrow{CHO+CHE}$ Cholestene-3-one + Fatty acid + H_2O_2

$2H_2O_2$ + 4-AAP + Phenol $\xrightarrow{POD}$ Quinoneimine (red) dye + $4H_2O$

3.12 Histopathological studies

After 28 days of daily dosing with 1g/kg body weight, the mice were sacrificed after anesthesiology in chloroform and organ tissue pieces harvested for histopathological examination. Tissues were trimmed, oriented in cassettes and fixed in buffered formalin while waiting for further processing in the automatic tissue processor. The organs collected were the kidney, liver, lung, heart, spleen, brain and testis. In the automatic

tissue processor, tissues in cassettes were further fixed for 2 hours in 40 % formalin then dehydrated in ascending grades of ethylalcohol starting with 40 %, 70 %, 95 % and two changes of absolute alcohol. At every stage, tissues were agitated for 2 hours. Clearing was done using Xylene before infiltrating in molten paraffin wax.

The infiltrated tissues were embedded in molten paraffin wax (external blocking) in base moulds, and then sliced into 0.5µm using a rotary microtome, floated in warm water at 55ºC and fished onto a microscope slide at an angle of 45º. The sections were held in hot air oven for 30 minutes to dewax excess paraffin wax before clearing in three changes of Xylene. Hydration in descending grades of alcohol, two changes of absolute alcohol, 95 %, 70 %, 50 % and finally in distilled water was done before staining in Hematoxylin and Eosin dyes using standard histological protocols. The stained tissues were mounted in DPX, cover slipped, dried and examined for pathological changes and photographed

3.13. Data Management and Statistical Analysis

In the *in vivo* hypoglycemic assays, unpaired students t-test, one way ANOVA and post ANOVA was used to analyze the significant difference between means of extracts treated animals, the diabetic control, insulin treated (standard control) and the normal control. The data was expressed as mean ± SD (standard Deviation). The probability value less than 0.05 ($p < 0.05$) was considered significant.

CHAPTER FOUR

RESULTS

4.1 Effects of oral and intraperitoneal administration of the five aqueous plants extracts at therapeutic doses to alloxan induced diabetic mice on blood glucose levels

4.1.1 Effects of oral and intraperitoneal administration of aqueous extracts at therapeutic doses of *Chasmanthera dependens* to alloxan induced diabetic mice on blood glucose levels

The yield of the freeze dried aqueous whole stem extract of *C. dependens* was 1.15 %, (13.8 g w/w) extracted from 1200g of ground powder. Oral administration of aqueous extracts of *C. dependens* to alloxan induced diabetic mice at 48.4, 93.5, 180.9, and 350 mg/kg body weight lowered blood glucose significantly to levels similar to those of the reference drug, glibenclamide from the second to the six hour (Figure 4.1). However, this reduction in blood glucose in alloxan induced diabetic mice within the same time periods was significantly higher than that of aqueous extracts of *C. dependens* at 25 mg/kg body weight dose ($\rho \leq 0.05$). In the eighth hour, all the five aqueous extract doses including the reference drug, glibenclamide, had lowered blood glucose of alloxan induced diabetic mice to similar levels to those of the normal control mice ($\rho > 0.05$); thereafter, the blood glucose levels of the alloxan induced diabetic mice rose towards the diabetic state levels which were similar for all the five extract doses including the reference drug, glibenclamide ($\rho > 0.05$) (Table 4.1; Figure 4.1).

In the second hour, intraperitoneal administration of aqueous extracts of *C. dependens* to alloxan induced diabetic mice at 25, 48.4, 93.5, 180.9, and 350 mg/kg body weight lowered blood glucose to similar levels which were comparable to those induced by the

reference drug, insulin ($\rho > 0.05$). This blood glucose level which was similar to that of the normal control mice induced by all the five extract doses including the reference drug, insulin, was maintained up to the twenty-fourth hour ($\rho > 0.05$) (Table 4.1; Figure 4.2).

Intraperitoneal administration of all the five aqueous extract doses of *C. dependens* to alloxan induced diabetic mice significantly ($\rho \leq 0.05$) reduced blood glucose levels to levels lower than those induced by the same five extract doses orally administered to alloxan induced diabetic mice in the second, fourth, sixth and the twenty-fourth hour (Table 4.1). At the eighth hour, oral administration of aqueous extracts of the five doses of *C. dependens* to alloxan induced diabetic mice reduced blood glucose to levels similar to those attained by the five aqueous extract doses of *C. dependens* administered intraperitoneally ($\rho > 0.05$).

Table 4.1.1: Effects of oral and intraperitoneal administration of aqueous extracts at therapeutic doses of *Chasmanthera dependens* to alloxan induced diabetic mice on blood glucose levels

Treatment	Route	Glucose levels at different hours after treatment					
		0hr	2hrs	4hrs	6hrs	8hrs	24hrs
Normal control	**Oral**	**5.3±0.2^{Aa}**	**5.2±0.1^{Aa}**	**5.3±0.1^{Aa}**	**5.2±0.1^{Aa}**	**5.2±0.1^{Aa}**	**5.2±0.1^{Aa}**
	IP	5.2±0.1^{Aa}	5.2±0.1^{Aa}	5.1±0.1^{Aa}	5.1±0.1^{Aa}	5.0±0.2^{Aa}	5.1±0.1^{ABa}
Diabetic plus Saline	**Oral**	**15.5±5.2^{Ca}**	**17.3±5.4^{Ba}**	**18.5±5.5^{Ca}**	**19.8±5.0^{Ba}**	**21.4±4.2^{Ba}**	**22.8±4.1^{Ca}**
	IP	12.6±1.8^{BCa}	14.0±1.4^{Bab}	15.4±1.4^{Babc}	17.0±1.4^{Bbc}	20.7±2.4^{Bcd}	18.5±1.8^{Cd}
Diabetic plus Gliben/insulin	**Oral**	**15.2±6.1^{Cb}**	**11.5±5.0^{ABab}**	**10.1±4.4^{ABab}**	**8.0±2.9^{Aab}**	**5.7±1.0^{Aa}**	**7.4±0.8^{ABa}**
	IP	13.7±2.9^{Cb}	5.6±0.7^{Aa}	4.9±0.3^{Aa}*	4.8±0.3^{Aa}	7.0±1.1^{Aa}	4.7±0.3^{Aa}
Extract dose (mg/kg body weight)							
25	**Oral**	**17.1±4.5^{Cb}**	**14.8±3.6^{Bab}**	**12.8±3.7^{BCab}**	**11.4±3.8^{Aab}**	**8.7±2.3^{Aa}**	**10.6±2.5^{Bab}**
	IP	9.4±0.7^{Bb}*	4.0±0.5^{Aa}*	3.6±0.8^{Aa}*	3.8±1.2^{Aa}*	3.6±0.2^{Aa}*	3.4±0.2^{Aa}*
48.4	**Oral**	**15.2 ±3.9^{Cb}**	**12.2 ±4.2^{ABab}**	**9.5 ±3.1^{ABab}**	**8.3 ±3.7^{Aab}**	**6.5 ±1.8^{Aa}**	**10.2 ±2.7^{Bab}**
	IP	11.8±0.6^{BCb}	4.1±0.6^{Aa}*	4.0±0.8^{Aa}*	3.8±1.0^{Aa}	4.5±1.2^{Aa}	3.5±0.7^{Aa}*
93.5	**Oral**	**14.9 ±5.8^{ABb}**	**11.7 ±4.9^{ABab}**	**8.5 ±3.9^{ABab}**	**6.8 ±0.5^{Aa}**	**5.1 ±1.0^{Aa}**	**10.2 ±1.5^{Bab}**
	IP	12.8±1.1^{BCb}	5.4±1.1^{Aa}*	4.5±0.7^{Aa}	4.2±0.7^{Aa}	4.0±1.2^{Aa}	4.3±0.9^{Aa}*
180.9	**Oral**	**13.6 ±3.3^{Abc}**	**10.8 ±2.3^{ABbc}**	**8.8 ±1.5^{ABab}**	**7.4 ±0.7^{Aa}**	**5.6 ±1.1^{Aa}**	**8.7 ±1.8^{ABab}**
	IP	12.5±3.5^{BCb}	7.0±6.3^{Aa}	4.2±1.0^{Aa}*	3.8±0.9^{Aa}*	3.7±1.2^{Aa}*	3.3±1.0^{Aa}*
350	**Oral**	**16.9 ±4.1^{Cc}**	**14.2 ±2.9^{Bbc}**	**11.8±2.3^{ABCbc}**	**9.1 ±3.5^{Aab}**	**6.1 ±1.4^{Aa}**	**9.9 ±1.9^{ABab}**
	IP	13.9±2.6^{Cb}	5.6±2.5^{Aa}*	4.3±2.3^{Aa}*	3.8±1.1^{Aa}*	3.6±1.9^{Aa}*	4.2±2.1^{Aa}*

Results expressed as Mean ± SD. Values in respective columns followed by similar upper case letters across treatments and values in respective rows followed by similar lower case letters are not significantly different ($\rho > 0.05$). Values before an* are significantly different in route of administration ($\rho \leq 0.05$).

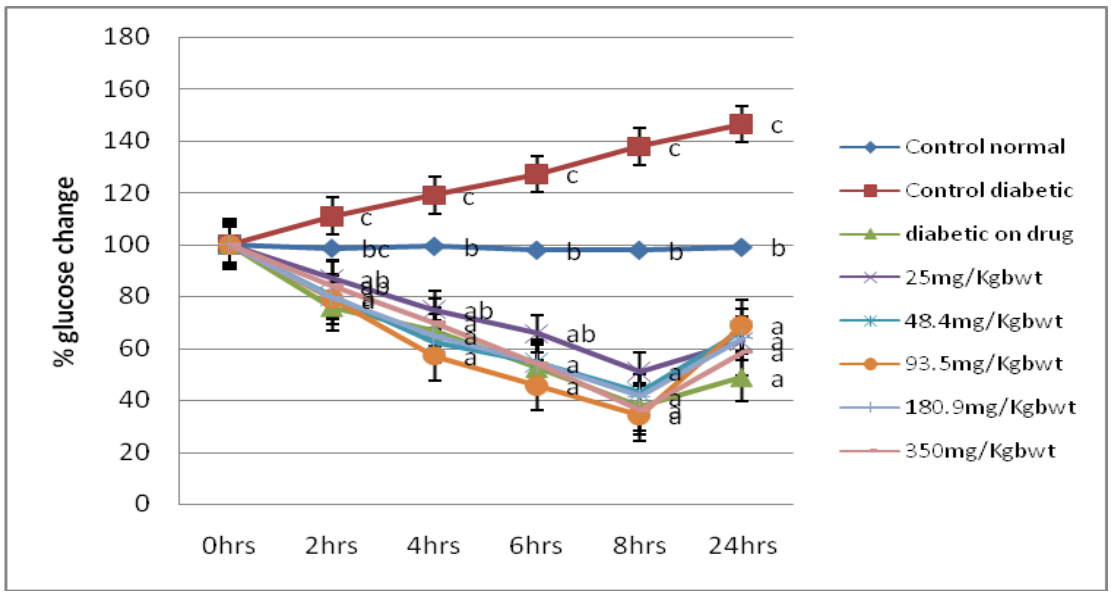

Figure 4.1: Percentage change in blood glucose levels after oral administration of aqueous extracts at therapeutic doses of *C. dependens* to alloxan induced diabetic mice.

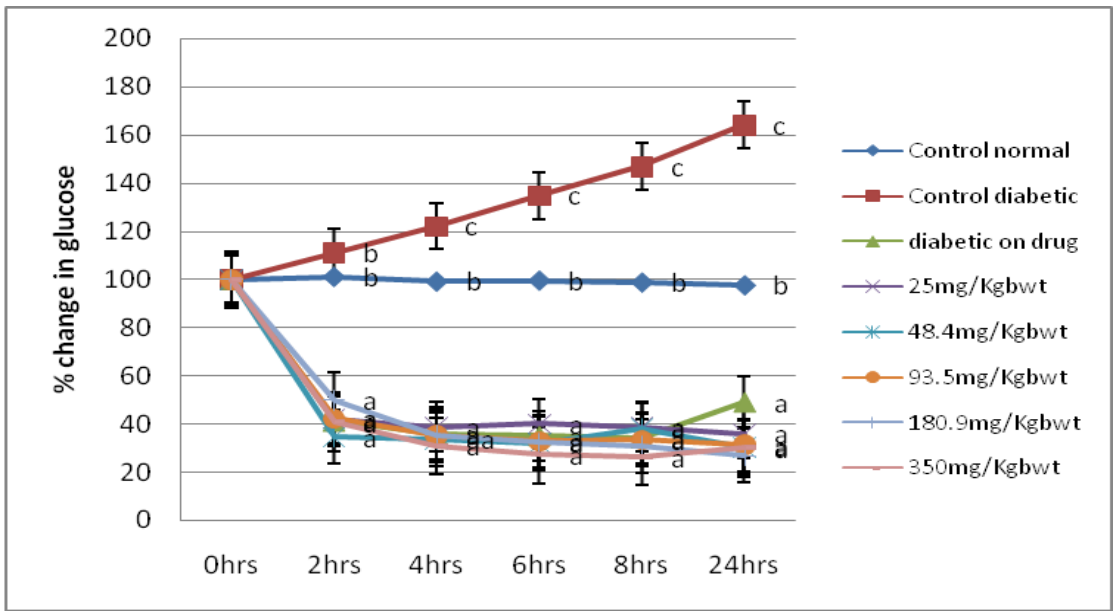

Figure 4.2: Percentage change in blood glucose levels after intraperitoneal administration of aqueous extracts at therapeutic doses of *C. dependens* to alloxan induced diabetic mice.

4.1.2 Effects of oral and intraperitoneal administration of aqueous extracts at therapeutic doses of *Mayrtenus undata* to alloxan induced diabetic mice on blood glucose levels.

Oral administration of aqueous stem bark extracts of *M. undata* to alloxan induced diabetic mice at 25 and 93.5 mg/kg body weight lowered blood glucose to levels comparable to those of the alloxan induced diabetic control mice in the second hour (Figure 4.3). However, the effects of oral administration of aqueous extracts of *M. undata* at 25, 48.4, 93.5, 180.9 and 350 mg/kg body weight on blood glucose to alloxan induced diabetic mice were statistically similar to those of the reference drug, glibenclamide ($\rho > 0.05$). The effects of oral administration of aqueous extracts of *M. undata* at doses of 93.5 and 180.9 mg/kg body weight in the fourth hour in alloxan induced diabetic mice were reduced to similar levels which were statistically significant and lower than those induced by aqueous extracts at 48.4 and 350 mg/kg body weight and by the reference drug ($\rho \leq 0.05$).

In the sixth hour, blood glucose levels in alloxan induced diabetic mice at doses of 48.4, 93.5 and 350 mg/kg body weight were lowered to levels similar to those of the reference drug, glibenclamide ($\rho \leq 0.05$) which were higher than those in the diabetic mice administered with a dose of 180.9 mg/kg body weight. There was no significant reduction ($\rho \leq 0.05$) in blood glucose in the diabetic mice administered with aqueous extracts at 25mg/kg body weight. In the eighth hour, blood glucose levels in alloxan induced diabetic mice treated with extract doses of 93.5, 180.9 and 350mg/kg body weight including the reference drug, Glibenclamide, were lowered to levels comparable to those in control normal mice administered with normal saline. There was no significant change in blood glucose levels in alloxan induced diabetic mice administered with aqueous extracts at 25 mg/kg body weight; the

levels were similar to those in alloxan induced diabetic control mice administered with normal saline. Thereafter, the glucose levels in diabetic mice administered with aqueous extracts at 48.4, 93.5, 180.9 and 350 mg/kg body weight rose towards diabetic state from the eighth hour to the twenty-fourth hour to levels statistically different from those in the reference drug ($\rho \leq 0.05$). The alloxan induced diabetic mice administered with a dose of 25 mg/kg body weight maintained high blood glucose levels throughout the experiment period (Table 4.2; Figure 4.3).

Intraperitoneal administration of aqueous stem bark extracts of *M. undata* to alloxan induced diabetic mice at doses of 25 and 48.4 mg/kg body weight in the second hour reduced blood glucose to similar levels ($\rho > 0.05$) which were lower than those of the reference drug insulin whereas those treated with aqueous extracts at doses of 93.5, 180.9 and 350 mg/kg body weight including the reference drug reduced blood glucose levels to similar levels ($\rho > 0.05$). In the fourth, sixth and the eighth hour, all alloxan induced diabetic mice intraperitoneally administered with aqueous extract of *M. undata* at doses of 25, 48.4, 93.5, 180.9 and 350 mg/kg body weight reduced glucose to normal levels which were statistically similar to blood glucose levels in diabetic mice administered with the reference drug, insulin ($\rho > 0.05$). The normal blood glucose levels in diabetic mice administered with aqueous extracts of *M. undata* at doses of 93.5, 180.9 and 350 mg/kg body weight including the reference drug, insulin, was maintained to the twenty-fourth hour while the blood glucose levels in the diabetic mice treated with aqueous plant extracts at doses of 25 and 48.4 mg/kg body weight rose to similar levels towards diabetic state (Table 4.2; Figure 4.4).

Oral administration of aqueous extracts of *M. undata* at doses of 93.5 and 350 mg/kg body weight in the second and fourth hour and at doses of 25 and 93.5mg/kg body weight in the sixth and eighth hour reduced glucose to levels significantly different from those attained in the intraperitoneally administered mice ($\rho \leq 0.05$). However, oral and intraperitoneal administration of aqueous extracts of *M. undata* to alloxan induced diabetic mice at doses of 48.4 and 180.9 mg/kg body weight were not significantly different (> 0.05) at all time points of experimental period (Table 4.2).

Table 4.2: Effects of oral and intraperitoneal administration of aqueous extracts at therapeutic doses of *Mayrtenus undata* to alloxan induced diabetic mice on blood glucose levels

Treatment	Route	Glucose levels at different hours after treatment					
		0	2	4	6	8	24
Normal control	**Oral**	**5.2 ±0.1^{Aa}**	**5.1 ±0.1^{Aa}**	**5.1 ±0.1^{Aa}**	**4.9 ±0.2^{Aa}**	**5.1 ±0.1^{Aa}**	**5.2 ±0.1^{Aa}**
	IP	5.2±0.1^{Aa}	5.2±0.1^{Aa}	5.2±0.1^{Aa}	5.2±0.1^{Aa}*	5.2±0.1^{Aa}	5.2±0.1^{Aa}
Diabetic plus Saline	**Oral**	**16.9 ±2.8^{Ba}**	**19.7±2.8^{Bab}**	**22.0 ±2.0^{Cbc}**	**24.1 ±1.9^{Cbc}**	**25.4±2.0^{Cb}**	**26.3±2.0^{Cb}**
	IP	12.7±1.7^{Ba}	14.3±1.5^{Cab}*	15.5±1.3^{Bbc}*	16.6±.9^{Bbc}*	18.1±1.1^{Bcd}*	19.8±1.5^{Bd}*
Diabetic plus Gliben/insulin	**Oral**	**19.5 ±3.9^{Bc}**	**15.1 ±3.9^{ABbc}**	**10.1 ±1.9^{ABab}**	**7.8 ±2.0^{ABa}**	**5.5 ±0.5^{Aa}**	**7.4 ±1.1^{Aa}**
	IP	14.0±2.8^{Bb}*	6.3±0.8^{ABa}*	5.9±0.6^{Aa}*	5.5±0.5^{Aa}	5.3±0.3^{Aa}	6.5±0.5^{Aa}
Extract dose (mg/kg body weight)							
25	**Oral**	**17.1 ±1.8^{Ba}**	**16.8 ±1.7^{Ba}**	**15.9 ±1.4^{BCa}**	**16.2 ±1.1^{BCa}**	**16.9 ±2.2^{Ba}**	**17.7 ±2.0^{BCa}**
	IP	14.5±0.9^{Ba}	11.5±1.7^{ABa}	6.8±0.4^{Aa}*	5.0±0.4^{Aa}*	4.1±0.3^{Aa}*	11.8±1.3^{ABa}
48.4	**Oral**	**19.8 ±2.7^{Ba}**	**14.5 ±1.0^{ABa}**	**12.2 ±0.9^{ABa}**	**11.1 ±0.7^{ABa}**	**10.3 ±0.6^{ABa}**	**15.3 ±2.7^{ABa}**
	IP	12.0±1.6^{Bd*}	10.8±3.5^{ABbc}	8.2±0.6^{Aabc}	5.9±0.7^{Aab}	4.3±0.6^{Aa}	11.1±2.1^{ABc}
93.5	**Oral**	**18.2 ±6.2^{Bb}**	**17.9 ±7.7^{Bb}**	**13.7 ±5.8^{ABCab}**	**8.7 ±2.4^{ABab}**	**6.6 ±1.4^{Aa}**	**14.5 ±6.5^{ABab}**
	IP	11.0±0.6^{Bd}*	5.6±2.0^{Abc}*	4.4±0.6^{Aabc}*	3.8±0.4^{Aab}*	3.4±0.5^{Aa}*	6.2±0.7^{Ac}*
180.9	**Oral**	**15.4 ±2.9^{Ba}**	**13.3 ±4.1^{ABa}**	**11.6±3.5^{ABCa}**	**10.3 ±2.7^{ABa}**	**5.9±3.0^{Aa}**	**11.1 ±3.3^{ABa}**
	IP	10.8±1.2^{Bd}*	5.7±1.7^{ABab}	4.7±1.1^{Aab}	4.3±0.8^{Aab}	3.9±1.0^{Aa}	6.5±0.8^{Ac}
350	**Oral**	**17.0 ±1.1^{Bb}**	**12.2 ±3.3^{ABab}**	**10.0 ±0.9^{ABab}**	**7.8 ±0.3^{Aab}**	**5.4 ±0.3^{Aa}**	**13.1 ±6.5^{ABab}**
	IP	12.4±2.7^{Bb}	6.3±1.9^{ABa}*	4.7±1.5^{Aa}*	4.6±1.5^{Aa}	4.3±1.0^{Aa}	5.7±1.2^{Aa}

Results expressed as Mean ± SD. Values in respective columns followed by similar upper case letters across treatments and values in respective rows followed by similar lower case letters are not significantly different ($\rho > 0.05$). Values before an* are significantly different in route of administration ($\rho \leq 0.05$).

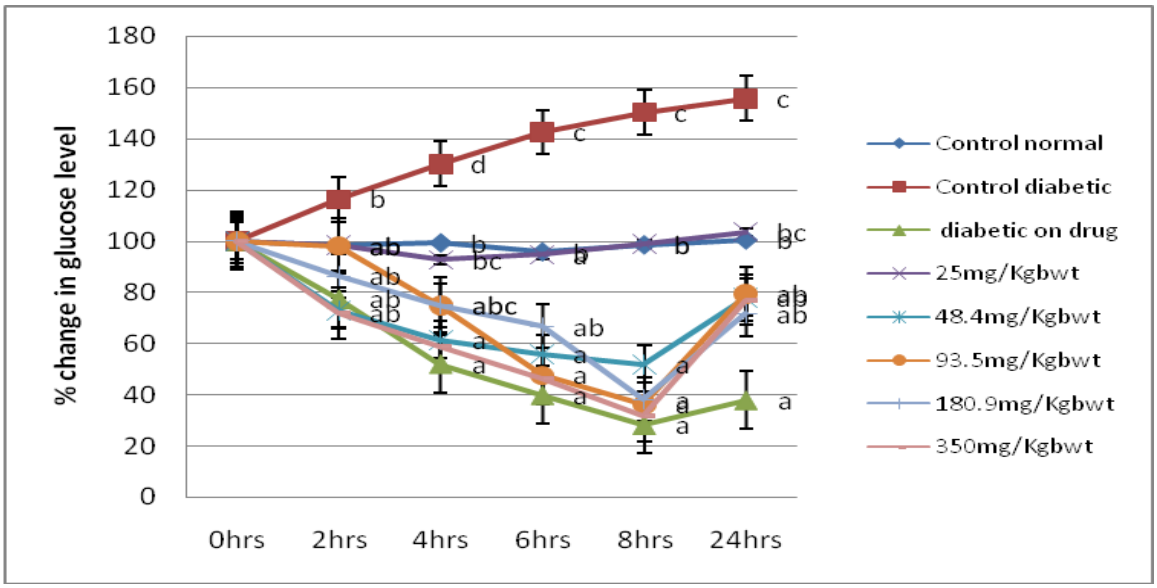

Figure 4.3: Percentage change in blood glucose levels after oral administration of aqueous extracts at therapeutic doses of *M. undata* to alloxan induced diabetic mice.

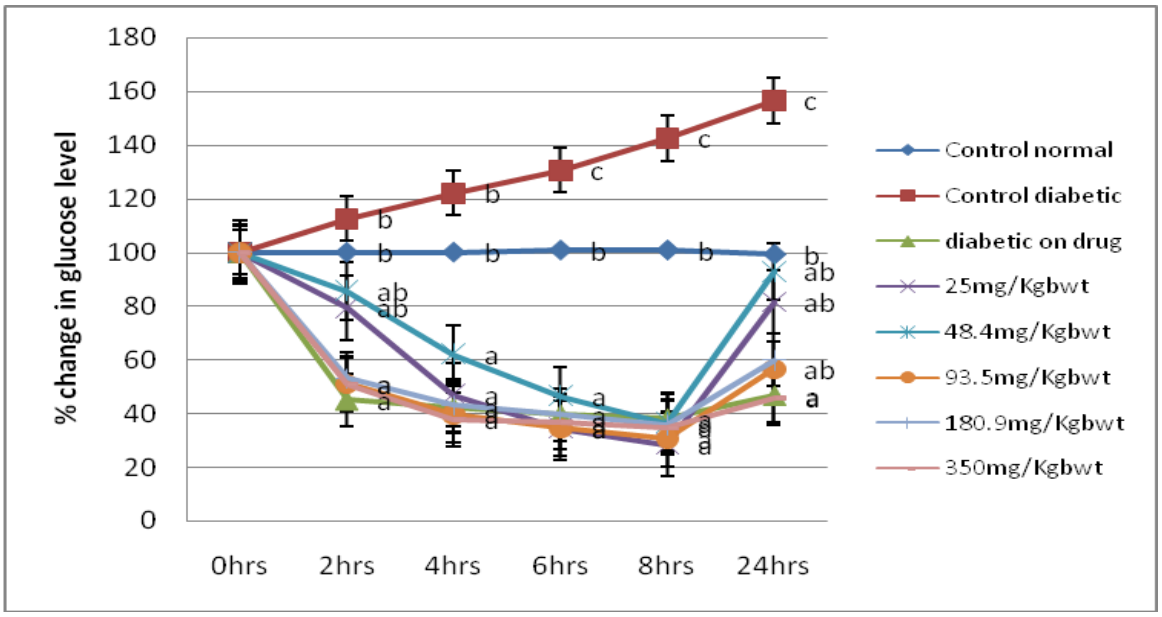

Figure 4.4: Percentage change in blood glucose levels after intraperitoneal administration of aqueous extracts at therapeutic doses of *M. undata* to alloxan induced diabetic mice.

4.1.3 Effects of oral and intraperitoneal administration of aqueous extracts at therapeutic doses of *Syzigium cordutum* to alloxan induced diabetic mice on blood glucose levels

Oral administration of aqueous stem bark extracts of *S. cordutum* to alloxan induced diabetic mice at doses of 25 and 48.4 mg/kg body weight in the second hour lowered blood glucose to similar levels which were significantly lower than those of the reference drug, Glibenclamide ($\rho \leq 0.05$). The blood glucose in diabetic mice administered with aqueous extracts at doses of 180.9 and 350 mg/kg body weight were lowered to similar levels which were comparable to the levels in diabetic mice administered with the reference drug, Glibenclamide ($\rho > 0.05$). The effects of aqueous extracts at a dose of 93.5 mg/kg body weight were significantly higher ($\rho \leq 0.05$) than the rest of the doses including the reference drug. In the fourth, sixth and eighth hour, the glucose levels in diabetic mice at doses of 93.5 and 180.9 mg/kg body weights were statistically similar to those of the reference drug. However, from the eighth to the twenty-fourth hour, the glucose levels in the five doses rose towards diabetic level (Table 4.3; Figure 4.5).

Intraperitoneal administration of aqueous extracts of *S. cordutum* at doses of 25, 48.4, 93.5 and 350 mg/kg body weight to alloxan induced diabetic mice in the second, fourth, sixth and eighth hour reduced blood glucose to levels lower than those of diabetic mice administered with the reference drug, insulin. The hypoglycemic effect of aqueous extract doses at 25, 48.4, 93.5 and 350 mg/kg body weight in the fourth and sixth hour were significantly higher ($\rho \leq 0.05$) than that of the reference drug. These levels then rose towards the diabetic state by the twenty-fourth hour.

Oral administration of aqueous extract doses of *S. cordutum* at doses of 48.4 and 93.5 mg/kg body weight to alloxan induced diabetic mice significantly reduced blood glucose ($\rho \leq 0.05$) to levels lower than those induced by the similar doses administered intraperitoneally to diabetic mice in the second, fourth, sixth and the eighth hour whereas those administered with aqueous extract doses at 180.9 and 350 mg/kg body weight reduced glucose to levels attained in the intraperitoneal route within the same time ($\rho > 0.05$) (Table 4.3).

Table 4.3: Effects of oral and intraperitoneal administration of aqueous extracts at therapeutic doses of *Syzigium cordutum* to alloxan induced diabetic mice on blood glucose levels

Treatment	Route	Glucose levels at different hours after treatment (mM)					
		0	2	4	6	8	24
Normal control	**Oral**	**5.1±0.1^{Aa}**	**5.2±0.1^{Aa}**	**5.2±0.0^{Aa}**	**5.1±0.1^{Aa}**	**5.2±0.1^{Aa}**	**5.2±0.1^{Aa}**
	IP	5.1±0.1^{Aa}	5.2±0.1^{Aa}	5.2±0.1^{ABa}	5.2±0.1^{ABa}	5.2±0.1^{ABa}	5.2±0.1^{Aa}
Diabetic plus Saline	**Oral**	**16.5±4.4^{BCa}**	**19.6±4.0^{CDab}**	**21.4±2.9^{Cabc}**	**23.4±2.8^{Dbc}**	**25.2±1.8^{Cbc}**	**26.7±2.2^{Dc}**
	IP	12.2±1.8^{ABa}	14.6±2.0^{BCab}*	15.8±1.9^{Cab}*	18.1±2.1^{Cbc}*	20.6±2.0^{Ccd}*	22.7±2.1^{Bd}*
Diabetic plus Gliben/insulin	**Oral**	**19.1±5.1^{BCc}**	**14.3±5.1^{ABCDbc}**	**10.6±4.4^{ABab}**	**6.6±1.6^{ABa}**	**5.2±0.6^{Aa}**	**7.5±0.9^{ABab}**
	IP	12.0±1.4^{ABc}*	6.1±0.6^{ABab}*	5.5±0.5^{ABa}*	5.1±0.2^{ABa}	5.1±0.1^{ABa}	7.3±0.6^{Ab}
Extract dose (mg/kg body weight)							
25	**Oral**	**12.9±3.0^{ABa}**	**12.3±4.9^{ABCa}**	**13.0±4.3^{ABCa}**	**12.0±3.7^{Ca}**	**11.1±4.1^{Ba}**	**13.3±3.3^{BCabc}**
	IP	15.3±5.0^{Bb}	8.5±3.6^{ABab}	5.7±0.7^{ABa}*	4.1±1.0^{ABa}*	2.6±1.1^{Aa}*	10.3±6.0^{Aab}
48.4	**Oral**	**21.4±8.3^{Cc}**	**18.6±6.0^{Dbc}**	**15.0±7.2^{BCbc}**	**10.5±4.1^{BCab}**	**7.2±2.2^{ABa}**	**15.2±6.7^{Cab}**
	IP	14.8±7.6^{ABc}	6.5±4.3^{ABab}*	4.8±1.9^{ABab}*	3.9±1.3^{Aa}*	3.1±0.7^{Aa}*	12.0±3.1^{Abc}
93.5	**Oral**	**13.9±3 .8^{ABCc}**	**9.4±1.7^{ABb}**	**7.1±1.0^{Aab}**	**6.5±0.9^{ABab}**	**5.0±1.1^{Aa}**	**8.7±2.0^{ABab}**
	IP	10.9±1.4^{ABb}	4.1±1.1^{Aa}*	3.7±0.7^{Aa}*	2.9±0.5^{Aa}*	3.2±0.4^{Aa}*	11.0±0.6^{Ab}*
180.9	**Oral**	**26.2±2.3^{BCb}**	**23.1±2.4^{BCDab}**	**17.1±5.6^{ABab}**	**12.9±4.7^{ABCab}**	**10.8±2.9^{ABa}**	**17.4±4.3^{BCab}**
	IP	20.4±1.0^{Ba}	17.0±1.1^{Ca}	12.4±1.1^{BCa}	9.6±0.7^{Ba}	8.2±0.8^{Ba}	13.9±1.2^{ABa}
350	**Oral**	**14.0±4.5^{ABCb}**	**12.3±4.1^{ABCab}**	**10.3±3.0^{ABab}**	**8.4±2.1^{ABCab}**	**7.5±2.0^{ABa}**	**9.5±1.8^{ABab}**
	IP	15.2±8.1^{ABb}	6.5±4.7^{ABab}	6.0±4.6^{ABa}	5.1±4.0^{ABa}	3.5±0.5^{Aa}	12.4±2.7^{Aab}*

Results expressed as Mean ± SD. Values in respective columns followed by similar upper case letters across treatments and values in respective rows followed by similar lower case letters are not significantly different ($\rho > 0.05$). Values before an* are significantly different in route of administration (≤ 0.05).

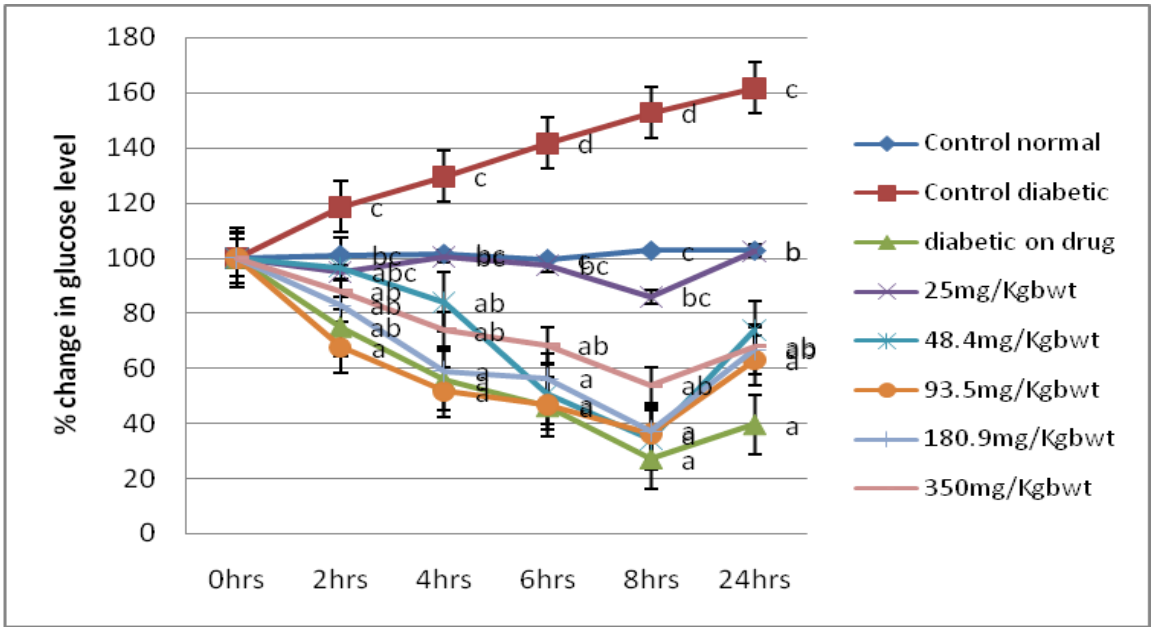

Figure 4.5: Percentage change in blood glucose levels after oral administration of aqueous extracts at therapeutic doses of *S. cordutum* to alloxan induced diabetic mice.

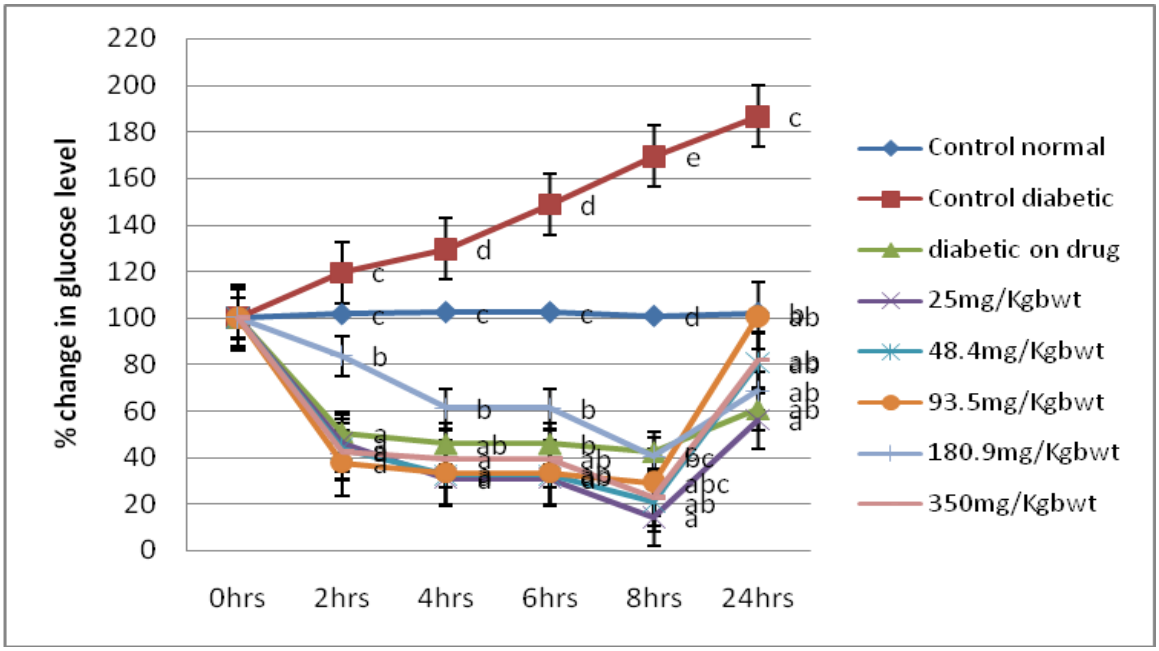

Figure 4.6: Percentage change in blood glucose levels after intraperitoneal administration of aqueous extracts at therapeutic doses of *S. cordutum* to alloxan induced diabetic mice.

4.1.4 Effects of oral and intraperitoneal administration of aqueous extracts at therapeutic doses of *Maerua subcordata* to alloxan induced diabetic mice on blood glucose levels

Blood glucose levels in alloxan induced diabetic mice orally administered with aqueous extracts of *M. subcordata* at 25, 48.4 and 350 mg/kg body weight in the second hour were reduced to similar levels which were significantly similar to those of the reference drug glibenclamide ($\rho > 0.05$) while those treated with 93.5 and 180.9 mg/kg body weight increased blood glucose to levels which were significantly different ($\rho \leq 0.05$) from those of the reference drug, Glibenclamide. In the fourth hour, blood glucose in the alloxan induced diabetic mice orally administered with aqueous extracts of *Maerua subcordata* at 25 and 48.4 mg/kg body weight were reduced to similar levels which were significantly lower ($\rho \leq 0.05$) than those of the reference drug, Glibenclamide while those in alloxan induced diabetic mice treated with doses of 180.9 and 350 mg/kg body weight were reduced to similar values which were comparable to those of diabetic mice administered with the reference drug ($\rho > 0.05$). The blood glucose in alloxan induced diabetic mice administered with a dose of 93.5 mg/kg body weight was raised to values which were significantly higher than those of the negative control administered with normal saline (Figure 4.7).

Further, in the sixth hour, blood glucose in alloxan induced diabetic mice orally administered with aqueous extracts of *M. subcordata* at doses of 25, 48.4, 180 and 350 mg/kg body weight decreased to statistically similar levels which were lower than those of the reference drug treated mice ($\rho \leq 0.05$). The glucose levels in alloxan induced diabetic mice administered with a dose of 93.5 mg/kg body weight were still higher

than the initial levels. In the eighth hour, the blood glucose levels in alloxan induced diabetic mice orally administered with aqueous extracts of *M. subcordata* at doses of 25, 48.4, 93.5, 180.9 and 350 mg/kg body weight reduced blood glucose to similar levels which were lower than those of the reference drug ($\rho \leq 0.05$). From the eighth to the twenty-fourth hour, the blood glucose levels in the alloxan induced diabetic mice administered with doses of 25, 48.4, 93.5, 180 and 350 mg/kg body weight rose to values significantly different from those of the reference drug ($\rho \leq 0.05$). The blood glucose levels in the alloxan induced diabetic mice subjected to doses of 25, 48.4 and 350 mg/kg body weight reduced the glucose levels to similar values which were lower than those of the reference drug treated mice ($\rho \leq 0.05$). Blood glucose in alloxan induced diabetic mice administered with a dose of 93.5 mg/kg body weight raised the blood glucose to values statistically similar to those of the negative control mice ($\rho > 0.05$), (Table 4.4; Figure 4.7).

Intraperitoneal administration of aqueous extracts of *M. subcordata* to alloxan induced diabetic mice at 25, 48.4 93.5, 180.9 and 350 mg/kg body weight reduced blood glucose levels to levels lower than those of the reference drug insulin from the second to the twenty-fourth hour ($\rho \leq 0.05$). However, the glucose levels in alloxan induced diabetic mice administered with aqueous extracts of *M. subcordata* at 25 mg/kg body weight was lower than those at 48.4, 93.5, 180.9 and 350 mg/kg body weight (Table 4.4; Figure 4.8).

Oral administration of aqueous extracts of *M. subcordata* to alloxan induced diabetic mice at 25, 48.4 93.5, 180.9 and 350 mg/kg body weight reduced blood glucose levels in the fourth, sixth and eighth hour to levels similar to those attained in the intraperitoneally administered mice ($\rho > 0.05$). However, blood glucose levels in alloxan induced diabetic mice intraperitoneally administered with aqueous extracts at 93.5 mg/kg body weight in the second and the twenty-fourth hour were significantly different ($\rho \leq 0.05$) from those attained in orally administered mice (Table 4.4).

Table 4.4 Effects of oral and intraperitoneal administration of aqueous extracts at therapeutic doses of *Maerua subcordata* to alloxan induced diabetic mice on blood glucose levels

Treatment	Route	Glucose levels at different hours after treatment (mmol/L)					
		0	2	4	6	8	24
Normal control	**Oral**	**5.2 ±0.2^{Aa}**	**5.2 ±0.1^{Aa}**	**5.2 ±0.2^{Aa}**	**5.2 ±0.1^{Aa}**	**5.2 ±0.2^{Aa}**	**5.2 ±0.2^{Aa}**
	IP	5.1±0.1^{Aa}	5.1±0.1^{Aa}	5.1±0.1^{Aa}	5.2±0.0^{ABa}	5.1±0.1^{Aa}	5.1±0.1^{Aa}
Diabetic plus Saline	**Oral**	**19.8 ±4.2^{Ba}**	**20.9 ±4.6^{Ba}**	**22.1 ±3.9^{Ca}**	**23.2 ±3.5^{Ba}**	**24.2 ±3.1^{Ba}**	**26 ±2.5^{Da}**
	IP	14.3±2.9^{Ba}	15.9±2.9^{Da}	17.3± 3.3^{Dab}	18.7±3.7^{Cab}	20.7±4.0^{Bab}	22.7±3.7^{Cb}
Diabetic plus Gliben/insulin	**Oral**	**18.3 ±4.2^{Bc}**	**13.4 ±4.5^{ABbc}**	**10.2±2.8^{ABCab}**	**7.2 ±0.7^{Aa}**	**4.7 ±0.5^{Aa}**	**7.6 ±1.6^{ABa}**
	IP	16.5±0.6^{Bc}	5.7±0.4^{ABa}*	5.5±0.5^{ABa}*	5.1±0.2^{Aa}*	4.8±0.1^{Aa}	7.8±0.8^{ABb}
Extract dose (mg/kg body weight)							
25	**Oral**	**13.5 ±2.5^{Ba}**	**12.3 ±6.1^{ABa}**	**9.7±4.4^{ABa}**	**8.3 ±3.7^{Aa}**	**6.8 ±1.2^{Aa}**	**12.7 ±5.2^{BCa}**
	IP	16.4±4.1^{Bb}	9.6±1.7^{ABCa}	7.6±0.6^{ABa}	7.1±0.8^{ABa}	6.3±±1.1^{Aa}	10.6±2.0^{Ba}
48.4	**Oral**	**14.0 ±5.2^{Ba}**	**11.4 ±4.3^{ABa}**	**9.2 ±3.2^{ABa}**	**9.8 ±5.0^{Aa}**	**7.7 ±2.7^{Aa}**	**11.7 ±4.1^{ABCa}**
	IP	12.6±3.1^{Bc}	10.0±2.3^{BCabc}	8.3±0.9^{ABCab}	7.6±0.6^{ABa}	7.3±0.5^{Aa}	11.3±1.4^{Bbc}
93.5	**Oral**	**12.0 ±3.0^{Ba}**	**18.1 ±5.8^{Ba}**	**15.8 ±6.8^{BCa}**	**13.8 ±3.4^{ABa}**	**10.7 ±6.1^{Aa}**	**17.0 ±4.9^{Ca}**
	IP	13.0±2.1^{Bc}	10.4±2.6^{BCbc}*	9.1±1.4^{BCab}	7.8±0.8^{ABab}	6.3±1.0^{Aa}	9.6±1.5^{Bb}*
180.6	**Oral**	**15.9 ±3.1^{Ba}**	**17.1 ±7.2^{Ba}**	**14.5 ±7.4^{ABCa}**	**13.1 ±7.4^{ABa}**	**9.9 ±5.3^{Aa}**	**17.1 ±4.1^{Ca}**
	IP	15.7±3.0^{Bc}	12.9±3.2^{CDbc}	11.8±3.1^{Cabc}	9.4±3.2^{Bab}	7.5±1.4^{Aa}	11.6±1.6^{Babc}*
350	**Oral**	**14.8 ±2.7^{Ba}**	**12.3 ±1.5^{ABa}**	**11.3 ±0.7^{ABCa}**	**11.9±0.6^{ABa}**	**9.9 ±0.2^{Aa}**	**12.4 ±1.7^{ABCa}**
	IP	14.8±4.1^{Bc}	10.1±2.5^{ABCabc}	8.2±1.6^{ABCab}	8.3±2.9^{ABab}	7.3±1.2^{Aa}	11.7±1.6A^{Bbc}

Results expressed as Mean ± SD. Values in respective columns followed by similar upper case letters and values in respective rows followed by similar lower case letters are not significantly different ($\rho > 0.05$). Values before an* are significantly different in route of administration ($\rho \leq 0.05$).

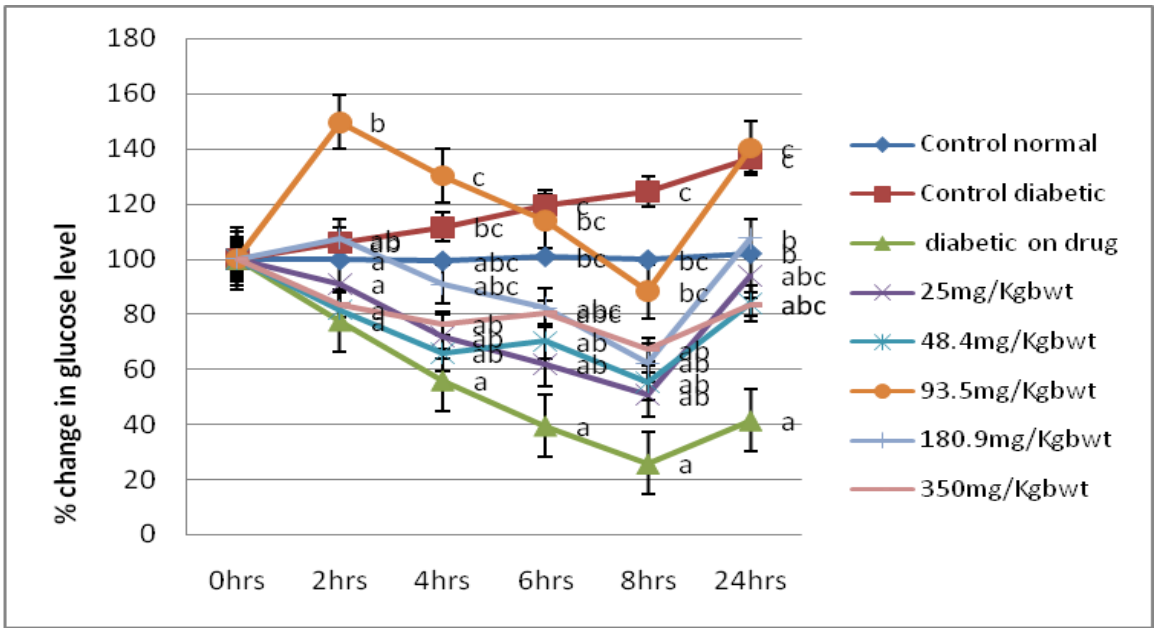

Figure 4.7: Percentage change in blood glucose levels after oral administration of aqueous extracts at therapeutic doses of *M. subcordata* to alloxan induced diabetic mice.

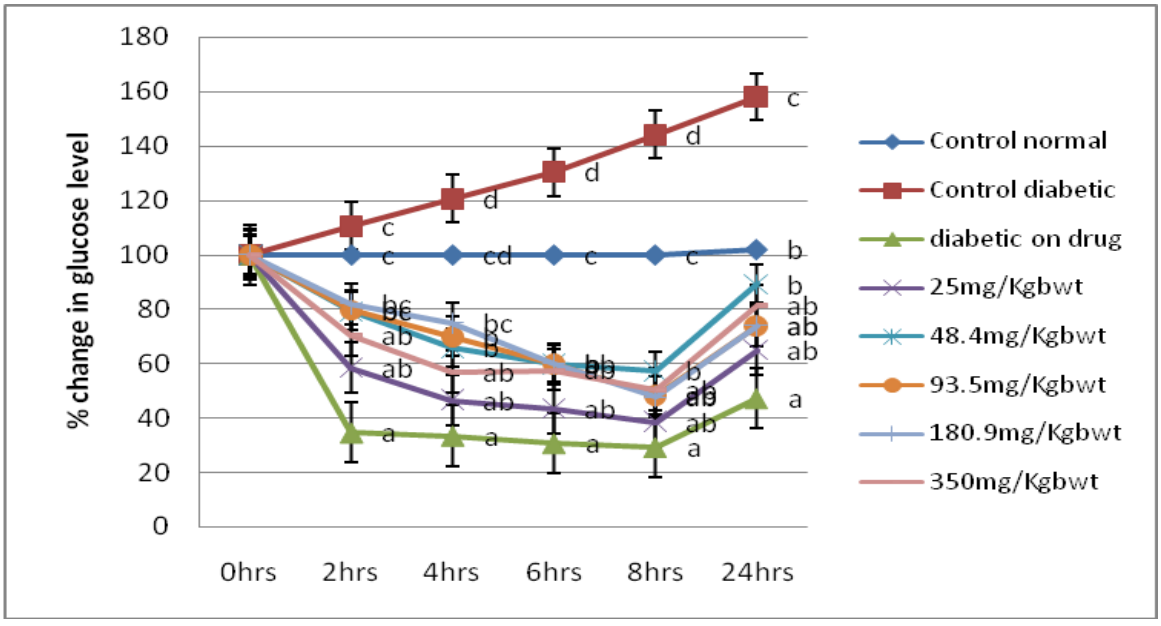

Figure 4.8: Percentage change in blood glucose levels after intraperitoneal administration of aqueous extracts at therapeutic doses of *M. subcordata* to alloxan induced diabetic mice.

4.1.5 Effects of oral and intraperitoneal administration of aqueous extracts at therapeutic doses of *Pappea capensis* to alloxan induced diabetic mice on blood glucose levels

Oral administration of aqueous stem bark extracts of *P. capensis* to alloxan induced diabetic mice at doses of 25, 48.4, 93.5 and 180.9 mg/kg body weight did not reduce blood glucose appreciably in the second hour. The glucose levels reduced to statistically similar levels which were significantly different ($\rho \leq 0.05$) from those of the reference drug. However those administered with a dose of 350 mg/kg body weight reduced blood glucose to significantly levels comparable to those of the reference drug ($\rho > 0.05$). Blood glucose levels in diabetic mice administered with aqueous stem bark extracts of *P. capensis* at doses of 25, 48.4, 93.5, 180.9 and 350 mg/kg body in the fourth, sixth, eighth and twenty-fourth-hour were lowered to statistically similar levels which were significantly different ($\rho \leq 0.05$) and lower than those of the reference drug. From the eighth to twenty-fourth hour, blood glucose levels in alloxan diabetic mice administered with aqueous extracts at doses of 93.5 and 350 mg/kg body weight rose towards the diabetic state; these levels were statistically similar to those of diabetic mice treated with doses of 25, 48.4 and 180.9 mg/kg body weights. Blood glucose in alloxan induced diabetic mice administered with the reference drug was significantly higher ($\rho > 0.05$) than levels of the aqueous extract treated diabetic mice (Table 4.5; Figure 4.9).

Intraperitoneal administration of aqueous extracts of *P. capensis* to alloxan induced diabetic mice at 25, 48.4, 93.5, 180.9 and 350 mg/kg body weight at the second, fourth, eighth and twenty-fourth hour lowered blood glucose to significantly similar levels ($\rho > 0.05$) which were lower than those of the reference drug, insulin ($\rho \leq 0.05$). Indeed there

was significant difference in blood glucose levels of the positive control mice and the extract treated diabetic mice (Table 4.5; Figure 4.10).

Oral administration of *P. capensis* extracts to diabetic mice at a dose of 25 mg/kg body weight in the second and fourth hour reduced blood glucose to significantly different levels ($\rho < 0.05$) from those attained in the intraperitoneally administered mice. With exception of the aqueous extract at a dose of 180 mg/kg body weight in the eighth hour, the rest of the doses at 48.4, 93.5 and 350 mg/kg body weight reduced blood glucose to significantly similar levels ($\rho > 0.05$) to those attained in the intraperitoneal route (Table 4.5).

Table 4.5: Effects of oral and intraperitoneal administration of aqueous extracts at therapeutic doses of *Pappea capensis* to alloxan induced diabetic mice on blood glucose levels

Treatment	Route	Glucose levels at different hours after treatment (mmol/L)					
		0	2	4	6	8	24
Normal control	**Oral**	**5.2 ±0.1^{Aa}**	**5.1 ±0.1^{Aa}**	**5.1 ±0.1^{Aa}**	**5.3±0.1^{Aa}**	**5.2±0^{Aa}**	**5.1±0.1^{Aa}**
	IP	5.1±0.1^{Aa}	5.1±0.1^{Aa}	5.2±0.1^{Aa}	5.2±0.1^{Aa}	5.2±0.1^{Aa}	5.2±0.1^{Aa}
Diabetic plus Saline	**Oral**	**17.6±3.8^{Ca}**	**20.5±3.2^{Cab}**	**22.8±2.3^{Babc}**	**24.2±2.4^{Bbc}**	**25.2±2.3^{Bbc}**	**26.1±2.1^{Bc}**
	IP	14.3±2.8^{Ba}	16.5±2.6^{Cab}	17.8±2.9^{Cabc*}	19.2±2.8^{Cabc*}	21.4±3.1^{Bbc}	23.0±2.9^{Dc}
Diabetic plus Gliben/insulin	**Oral**	**18.9±4.8^{Cc}**	**14.4±5.2^{Aab}**	**9.6±2.8^{Aa}**	**7.1±1.6^{Aa}**	**5.5±0.6^{Aa}**	**6.9±1.0^{Aa}**
	IP	13.6±3.3^{Bc}	6.4±0.7^{Cbc*}	5.7±0.5^{ABabc*}	5.1±0.3^{ABab*}	4.9±0.4^{Aa}	7.3±0.5^{ABa}
Extract dose (mg/kg body weight)							
25	**Oral**	**8.3±1.3^{ABa}**	**7.9±1.0^{ABa}**	**7.6±2.2^{Aa}**	**6.8±1.1^{Aa}**	**6.8±0.6^{Aa}**	**6.8±0.4^{Aa}**
	IP	15.9±4.2^{Bc*}	13.1±3.8^{Cbc*}	10.4±3.0^{ABabc}	8.4±1.9^{ABab}	7.3±1.0^{Aa}	11.5±2.6^{Cabc*}
48.4	**Oral**	**10.9±1.2^{BCa}**	**8.3±0.8^{ABCa}**	**7.2±0.9^{Aa}**	**6.5±1.6^{Aa}**	**7.0±0.7^{Aa}**	**7.0±1.7^{Aa}**
	IP	18.0±5.0^{Bc}	14.4±5.1^{Cab}	12.0±5.4^{BCab}	9.4±3.5^{Ba}	7.9±2.3^{Aa}	10.5±3.1^{BCab}
93.5	**Oral**	**13.5±4.1^{BCa}**	**12.4±5.5^{ABCa}**	**11.6±2.3^{Aa}**	**10.5±2.5^{Aa}**	**11.6±3.1^{Aa}**	**13.8±4.7^{Aa}**
	IP	16.2±5.1^{Bb}	12.5±4.7^{BCab}	10.4±3.7^{ABab}	7.9±2.4^{ABa}	6.8±2.1^{Aa}	10.6±2.0^{BCab}
180.6	**Oral**	**11.0±2.7^{ABCa}**	**9.6±1.8^{ABa}**	**9.9±3.0^{Aa}**	**8.1±1.9^{Aa}**	**7.5±1.7^{Aa}**	**7.4±1.8^{Aa}**
	IP	14.3±3.1^{Bc}	10.3±1.8^{ABCb}	7.3±1.5^{ABab}	6.1±1.1^{ABa}	5.3±0.7^{Aa*}	9.4±0.9^{BCb}
350	**Oral**	**12.6±4.7^{ABCa}**	**6.1±2.4^{ABa}**	**7.5±1.1^{Aa}**	**7.7±0.5^{Aa}**	**9.8±3.0^{Aa}**	**12.7±3.8^{Aa}**
	IP	14.8±4.4^{Bc}	10.2±3.5^{ABCbc}	7.4±2.0^{ABab}	5.5±0.8^{ABab}	4.9±0.8^{Aa}	8.5±0.9^{ABCab}

Results expressed as Mean ± SD. Values in respective columns followed by similar upper case letters across treatments and values in respective rows followed by similar lower case letters are not significantly different ($\rho > 0.05$). Values before an* are significantly different in route of administration ($\rho \leq 0.05$)

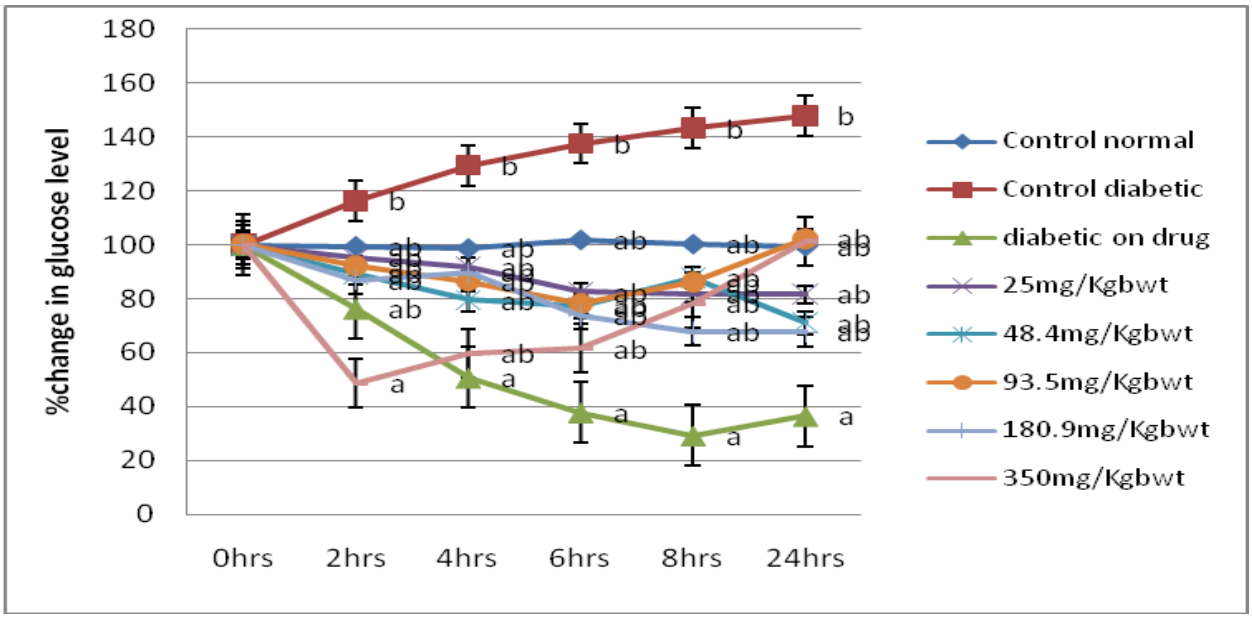

Figure 4.9: Percentage change in blood glucose levels after oral administration of aqueous extracts at therapeutic doses of *P. capensis* to alloxan induced diabetic mice.

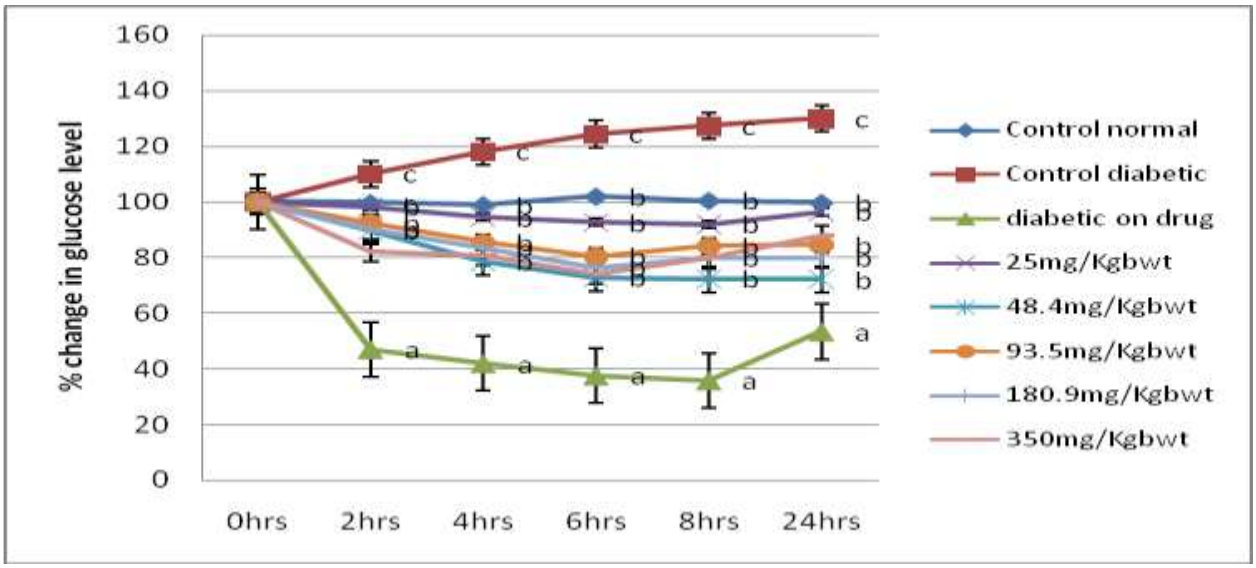

Figure 4.10: Percentage change in blood glucose level after intraperitoneal administration of aqueous extracts at therapeutic doses of *P. capensis* to alloxan induced diabetic mice.

4.2 Comparison of the effects of oral and intraperitoneal administration of the five aqueous plants extracts at a specific therapeutic dose to alloxan induced diabetic mice on blood glucose levels

4.2.1 Effects of oral and intraperitoneal administration of the five aqueous plants extracts at 25 mg/kg body weight to alloxan induced diabetic mice on blood glucose levels

Oral administration of aqueous extracts of *C. dependens, M. undata, S. cordatum, M. subcordata* and *P. capensis* to alloxan induced diabetic mice at 25 mg/kg body weight reduced blood glucose levels in the second hour to 95.2, 91.1, 95.3, 98.2 and 86.6 %, respectively. The most effective plant extract at 25 mg/kg body weight in the second hour was the extract from *C. dependens* which reduced blood glucose level to 86.6 %. However, the effects of aqueous extracts of C. *dependens* and *S. cordatum* at the second hour and those of *M. subcordata* and *M. undata* were statistically similar ($\rho > 0.05$). In the eighth hour, aqueous extracts of *M. subcordata* and *C. dependens* reduced glucose levels to 50 and 51.9 %, respectively in alloxan induced diabetic mice. The effects on blood glucose at this hour were significantly similar and higher than the rest of the three other plants extract (*P. capensis*, *S. cordatum* and *M. undata*) which reduced blood glucose levels to 81.9, 86 and 98.8 %, respectively. The reduction in blood glucose by aqueous extracts of *M. undata* to alloxan induced diabetic mice at the eighth hour was significantly lower ($p \leq 0.05$) than the rest of the plant extracts. Therefore, the most effective aqueous extract at lowering blood glucose levels at 25 mg/kg body weight over the experimental period was the extract from *C. dependens* (Table 4.6; Figure 4.11).

Intraperitoneal administration of aqueous plant extracts at this dose to alloxan induced diabetic mice had better activity with the most effective plant extract being *S. cordatum* which had a hypoglycemic activity of 85.8 % in the eighth hour. Aqueous extracts of *S. cordatum* in the fourth, sixth and eighth hour significantly lowered blood glucose levels in alloxan induced diabetic mice ($\rho < 0.05$). Intraperitoneal administration of aqueous extracts of *P. capensis*, *M. undata*, *M. subcordata* and *C. dependens* to alloxan induced diabetic mice reduced glucose levels to 48, 28.3, 38.4 and 38.3 %, respectively. However, the hypoglycemic effect of *C. dependens* extract in the twenty-fourth hour was significantly higher than that of the rest of the extracts ($\rho \leq 0.05$) (Table 4.7; Figure 4.12).

Table 4.6: Effects of oral administration of the five aqueous plants extracts at 25 mg/kg body weight to alloxan induced diabetic mice on blood glucose levels

Extract	0hrs	2hrs	4hrs	6hrs	8hrs	24hrs
P. capensis	8.3 ± 1.5^{Aa}	7.9 ± 1.0^{Aa}	7.6 ± 2.2^{Aa}	6.8 ± 1.1^{Aa}	6.8 ± 0.6^{Aa}	6.8 ± 0.4^{Aa}
M. subcordata	13.5 ± 2.5^{Aab}	12.3 ± 6.1^{ABb}	9.7 ± 4.4^{ABab}	8.3 ± 3.9^{BCa}	6.8 ± 1.2^{BCa}	12.7 ± 5.2^{Cb}
S. cordatum	12.9 ± 3.0^{Aab}	12.3 ± 4.9^{Aab}	13.0 ± 4.3^{Aab}	12.0 ± 3.7^{Ab}	11.1 ± 4.1^{Aa}	13.3 ± 3.3^{Ab}
M. undata	17.1 ± 1.8^{Ab}	16.8 ± 1.7^{Ab}	15.9 ± 1.4^{Ab}	16.2 ± 1.1^{Ab}	16.9 ± 2.2^{Ab}	17.7 ± 2.0^{Ac}
C. dependens	17.1 ± 4.5^{Db}	14.8 ± 3.6^{CDab}	12.8 ± 3.8^{BCab}	11.4 ± 3.8^{ABab}	8.7 ± 2.3^{Aa}	10.6 ± 2.5^{ABab}

Results expressed as Means ± SD. Values along time points followed by similar upper case letters and values across extracts followed by similar lower case superscript are not statistically different at $p \leq 0.05$.

Table 4.7: Effects of intraperitoneal administration of the five aqueous plants extracts at 25 mg/kg body weight to alloxan induced diabetic mice on blood glucose levels

Extract	0hrs	2hrs	4hr	6hrs	8hrs	24hrs
P. capensis	15.3 ± 5.0^{Ea}	13.2 ± 3.8^{Db}	10.4 ± 3.0^{BCb}	8.4 ± 1.9^{ABb}	7.3 ± 1.0^{Ab}	11.5 ± 2.7^{Dab}
M. subcordata	16.4 ± 4.1^{Bb}	9.6 ± 1.7^{Aab}	7.6 ± 0.6^{Aab}	7.1 ± 0.8^{Aab}	6.3 ± 1.1^{Ab}	10.6 ± 2.0^{ABb}
S. cordatum	18.3 ± 4.0^{Bb}	8.5 ± 4.4^{Aa}	5.7 ± 3.0^{Aa}	4.2 ± 2.8^{Aa}	2.6 ± 1.1^{Aa}	10.3 ± 1.3^{Ab}
M. undata	14.5 ± 4.9^{Bab}	11.5 ± 3.7^{ABab}	6.8 ± 2.0^{Aab}	5.0 ± 3.4^{Aab}	4.1 ± 2.1^{Aab}	11.8 ± 1.2^{ABb}
C. dependens	9.4 ± 0.7^{Bab}	4.0 ± 0.5^{Aa}	3.6 ± 0.8^{Aa}	3.8 ± 1.2^{Aa}	3.6 ± 0.2^{Aa}	3.4 ± 0.5^{Aa}

Results expressed as Means ± SD. Values along time points followed by similar upper case letters and values across extracts followed by similar lower case superscript are not statistically different at $p \leq 0.05$.

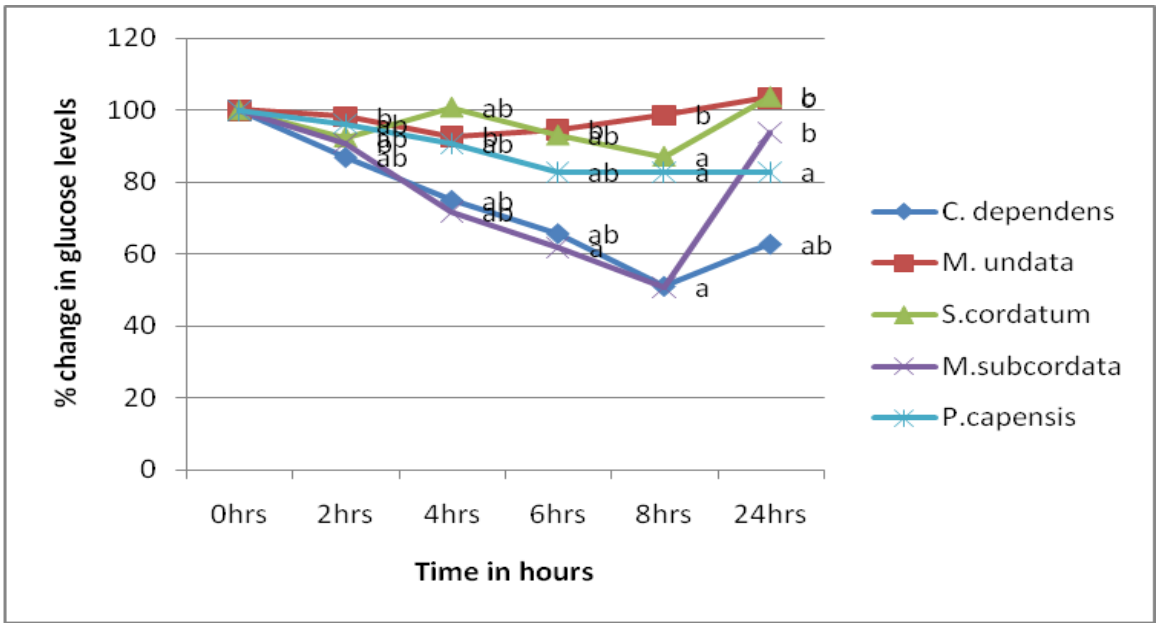

Figure 4.11: Percentage change in blood glucose levels after oral administration of the five aqueous plants extracts at 25mg/kg body weight to alloxan induced diabetic mice. Values at different time points with similar superscripts are not significantly different at $p \leq 0.05$.

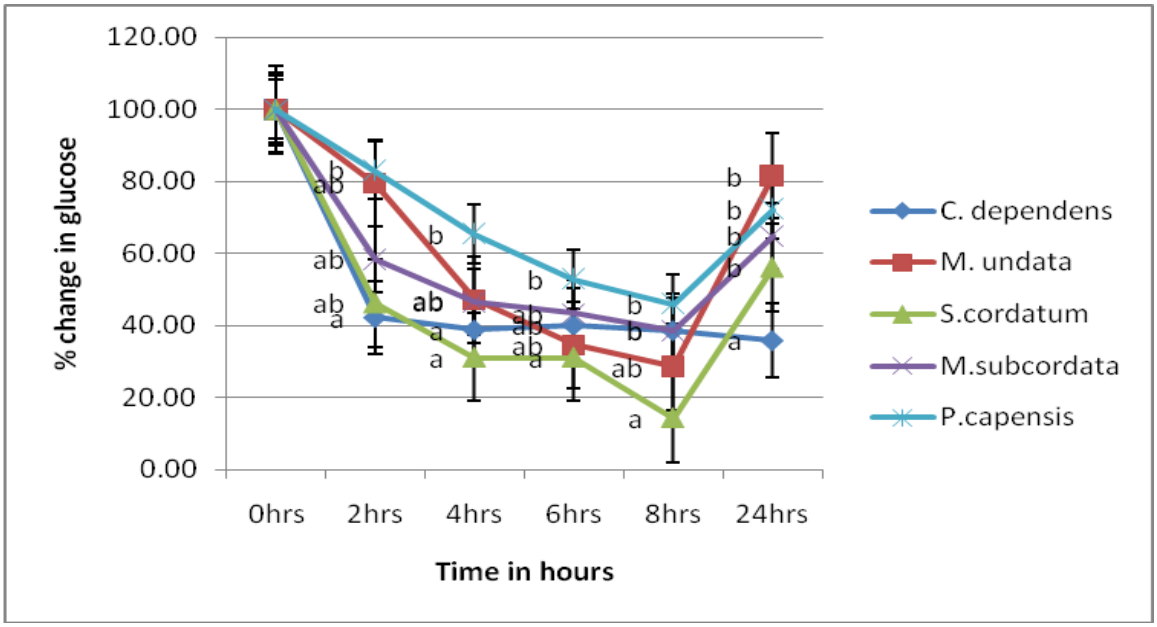

Figure 4.12: Percentage change in blood glucose levels after intraperitoneal administration of the five aqueous plants extracts at 25mg/kg body weight to alloxan induced diabetic mice. Values at different time points with similar superscripts are not significantly different at $p \leq 0.05$.

4.2.2 Effects of oral and intraperitoneal administration of the five aqueous plants extracts at 48.4 mg/kg body weight to alloxan induced diabetic mice on blood glucose levels

Oral administration of aqueous extracts of *C. dependens, M. undata, S. cordatum, M. subcordata* and *P. capensis* to alloxan induced diabetic mice at 48.4 mg/kg body weight reduced blood glucose levels to various degrees at various times (Table 4.5; Figure 4.13). Oral administration of the five aqueous plants extracts to alloxan induced diabetic mice at 48.4 mg/kg body weight caused a non-significant effect on blood glucose levels at the second, fourth, sixth and twenty-fourth hour ($\rho > 0.05$); the most effective extract in lowering blood glucose levels was that from *C. dependens*.

Intraperitoneal administration of aqueous extracts of *C. dependens, M. undata, S. cordatum, M. subcordata* and *P. capensis* to alloxan induced diabetic mice at 48.4 mg/kg body weight in the second hour lowered blood glucose levels to 36.7, 90, 43.9, 79.4 and 80 %, respectively. In the first two hours, intraperitoneal administration of aqueous plants extracts at the same dose reduced blood glucose levels by 63.3, 10.0, 56.1, 20.6 and 20.0 %, respectively. Four hours later, intraperitoneal administration of aqueous extracts of *C. dependens, M. undata, S. cordatum, M. subcordata* and *P. capensis* to alloxan induced diabetic mice reduced blood glucose levels to 33.9, 68.3, 32.4, 65.9 and 66.7 %, respectively. In the sixth hour, intraperitoneal administration of these extracts to alloxan induced diabetic mice had reduced blood glucose levels to 32.2, 39.9, 20.9, 57.9 and 43.9 %, respectively. Eight hours after intraperitoneal administration of the extracts to alloxan induced diabetic mice reduced blood glucose levels to 38.1, 35.8, 20.9, 57.9, and 43.9 %, respectively. Twenty-four hours later,

intraperitoneal administration of aqueous extracts of *C. dependens*, *S. cordatum*, *M. subcordata* and *P. capensis* to alloxan induced diabetic mice reduced blood glucose to 29.7, 81.1, 89.7 and 58.3 %, respectively, while intraperitoneal administration of aqueous extracts of *M. undata* had reverted blood glucose levels to that of the diabetic state. Intraperitoneal administration of aqueous extracts of *M. undata* and *C. dependens* to alloxan induced diabetic mice in the eighth hour caused a non-significant effect to the levels of blood glucose levels; the most effective extract in lowering blood glucose levels at this hour was that of *S. cordatum*. However in twenty-fourth hour, intraperitoneal administration of aqueous extracts of *C. dependens* to alloxan induced diabetic mice caused a significantly greater reduction in blood glucose levels compared to the rest of the extracts.

Overall, the most effective extract at this dose in both the oral and intraperitoneal route was *C. dependens*; the intraperitoneal route showed better activity compared to the oral route (Table 4.6; 4.9; Figure 4.13 and 4.14).

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Table 4.8: Effects of oral administration of the five aqueous plants extracts at 48.4 mg/kg body weight to alloxan induced diabetic mice on blood glucose levels

Extract	0hrs	2hrs	4hrs	6hrs	8hrs	24hrs
P. capensis	14.8 ± 5.5^{Aa}	13.2 ± 6.9^{Aa}	11.8 ± 6.3^{Aa}	11.4 ± 6.8^{Aa}	13.0 ± 8.2^{Aa}	10.5 ± 4.9^{Aa}
M. subcordata	14.0 ± 5.1^{Ea}	11.4 ± 4.3^{Da}	9.2 ± 3.2^{Ca}	9.8 ± 3.2^{ABa}	7.7 ± 2.8^{Aa}	11.7 ± 4.1^{BCa}
S. cordatum	23.4 ± 6.3^{Ca}	22.5 ± 7.1^{Ca}	19.6 ± 8.9^{Ca}	11.4 ± 2.2^{ABa}	8.0 ± 1.7^{Aa}	17.3 ± 5.2^{BCa}
M. undata	19.8 ± 4.3^{Ba}	14.5 ± 4.9^{ABa}	12.2 ± 4.4^{ABa}	11.1 ± 4.8^{ABa}	10.3 ± 4.3^{Aa}	15.5 ± 4.6^{ABa}
C. dependens	15.2 ± 5.9^{Da}	12.2 ± 4.2^{Ca}	9.5 ± 3.1^{CDa}	8.3 ± 3.7^{ABa}	6.5 ± 1.8^{Aa}	10.2 ± 2.7^{BCa}

Results expressed as Means ± SD. Values along time points followed by similar upper case letters and values across extracts followed by similar lower case superscript are not statistically different at $p \leq 0.05$.

Table 4.9: Effects of intraperitoneal administration of the five aqueous plants extracts at 48.4 mg/kg body weight to alloxan induced diabetic mice on blood glucose levels

Extract	0hrs	2hrs	4hrs	6hrs	8hrs	24hrs
P. capensis	18.0 ± 5.0^{Da}	14.4 ± 5.2^{Cb}	12.0 ± 5.4^{BCa}	9.4 ± 3.5^{ABb}	7.9 ± 2.3^{Ab}	10.5 ± 3.1^{ABa}
M. subcordata	12.6 ± 3.1^{Ba}	10.0 ± 2.3^{ABab}	8.3 ± 0.9^{ABa}	7.6 ± 0.6^{Aab}	7.3 ± 0.5^{Ab}	11.3 ± 1.4^{ABa}
S. cordatum	14.8 ± 7.6^{Ba}	6.5 ± 4.3^{Aab}	4.8 ± 1.9^{Aa}	3.9 ± 1.3^{Aa}	3.1 ± 0.7^{Aa}	12.0 ± 3.1^{Ba}
M. undata	12.0 ± 3.1^{Ba}	10.8 ± 1.1^{ABab}	8.2 ± 1.5^{ABa}	5.9 ± 4.1^{ABab}	4.3 ± 0.9^{Aa}	12.1 ± 10.3^{ABa}
C. dependens	11.8 ± 0.6^{Ba}	4.1 ± 0.6^{Aa}	4.0 ± 0.8^{Aa}	3.8 ± 0.9^{Aa}	4.5 ± 1.2^{Aa}	3.5 ± 0.7^{Aab}

Results expressed as Means ± SD for five mice per group. Values along time points followed by similar upper case letters and values across extracts followed by similar lower case superscript are not statistically different at $p \leq 0.05$.

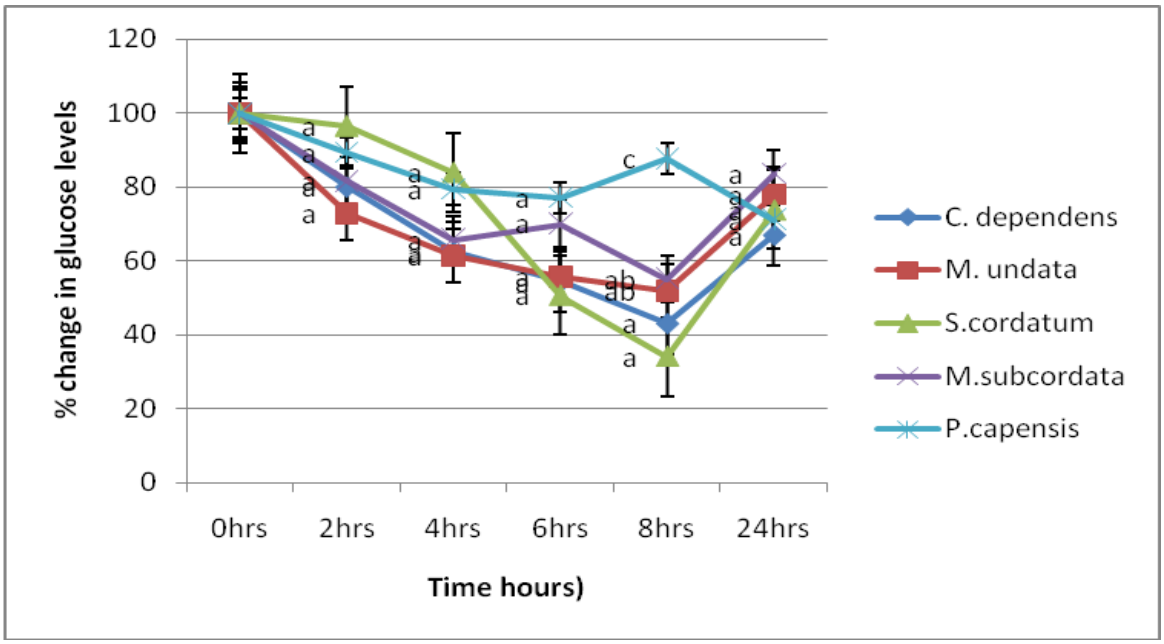

Figure 4.13: Percentage change in blood glucose levels after oral administration of the five aqueous plants extracts at 48.4 mg/kg body weight to alloxan induced diabetic mice. Values at different time points with similar superscript are not significantly different at $p \leq 0.05$.

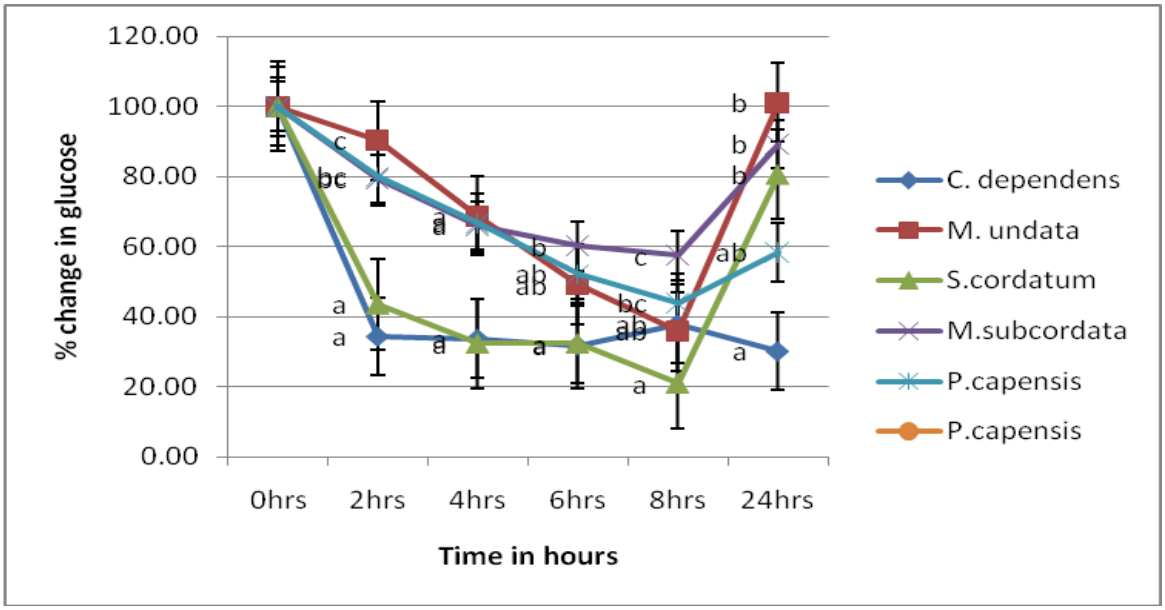

Figure 4.14: Percentage change in blood glucose levels after intraperitoneal administration of the five aqueous plants extracts at 48.4 mg/kg body weight to alloxan induced diabetic mice. Values at different time points with similar superscript are not significantly different at $p \leq 0.05$.

4.2.3 Effects of oral and intraperitoneal administration of the five aqueous plants extracts at 93.5 mg/kg body weight to alloxan induced diabetic mice on blood glucose levels

Oral administration of aqueous extracts of *C. dependens, M. undata, S. cordatum* and *P. capensis* to alloxan induced diabetic mice at 93.5 mg/kg body weight in the second hour lowered blood glucose levels to 78.5, 98.3, 68.1 and 91.8 %, respectively while those orally administered with aqueous extracts of *M. subcordata* increased the blood glucose levels to 150.8 %. In the fourth hour, oral administration of aqueous extracts *C. dependens, M. undata, S. cordatum* and *P. capensis* to alloxan induced diabetic mice reduced blood glucose levels to 57.1, 75.3, 51.5, and 85.9 %, respectively. Six hours later, oral administration of aqueous extracts of *M. subcordata* to alloxan induced diabetic mice raised blood glucose level to 115 %, while oral administration of aqueous extracts of *C. dependens, M. undata, S. cordatum* and *P. capensis* to alloxan induced diabetic mice reduced blood glucose levels to 45.6, 47.8, 47.8 and 77.8 %, respectively. In the eighth hour, oral administration of aqueous extracts of *C. dependens, M. undata, S. cordatum, M. subcordata* and *P. capensis* to alloxan induced diabetic mice reduced blood glucose levels to 34.2, 36.3, 36.2, 89.2and 85.9 %, respectively. Twenty-four hours later, oral administration of aqueous extracts of *M. subcordata* to alloxan induced diabetic mice raised the blood glucose levels to 141.7 %. Oral administration of the other three plant extracts to alloxan induced diabetic mice reduced blood glucose levels to 68.5, 79.7 and 62.6 %, respectively (Table 4.10; Figure 4.15).

Intrapreitoneal administration of the same plant extracts at the same dose to alloxan induced diabetic mice, lowered blood glucose levels appreciably from the second to the

eighth hour. In the second hour, intraperitoneal administration of aqueous extracts of *C. dependens, M. undata , S. cordatum, M. subcordata* and *P.capensis* to alloxan induced diabetic mice reduced blood glucose levels to 42.2, 50.9, 37.6, 80.0 and 77.2 %, respectively. By the sixth hour, the same plant extracts had lowered the blood glucose levels by 67.2, 65.4, 73.4, 40.0 and by 51.2 %. respectively. There was no significant difference in blood glucose levels between intraperitoneal administration of aqueous extracts of *C. dependens, M. undata* and *S. cordatum* to alloxan induced diabetic mice at the eighth hour, Twenty four hours later, intraperitoneal administration of aqueous extracts of *C.dependens M. undata, M. subcordata* and *P.capensis* to alloxan induced diabetic mice had reduced blood glucose levels by 68.8, 43.6 26.2 and 34.6 %, respectively, while *S. cordatum* had raised blood glucose levels to 109.2 %. At this time, the blood glucose levels induced by aqueous extracts of *C.dependens* were significantly higher than the rest of the extracts (Table 4:11; Figure 4.16).

Table 4.10: Effects of oral administration of the five aqueous plants extracts at 93.5 mg/kg body weight to alloxan induced diabetic mice on blood glucose levels

Extract	0hrs	2hrs	4hrs	6hrs	8hrs	24hrs
P. capensis	13.5 ± 4.7^{Aa}	12.4 ± 6.7^{Aa}	11.6 ± 7.3^{Aa}	10.5 ± 6.1^{Aa}	11.6 ± 8.8^{Aa}	13.8 ± 9.3^{Aa}
M. subcordata	12.0 ± 3.0^{Ba}	18.1 ± 5.8^{ABa}	15.8 ± 6.8^{ABa}	13.8 ± 6.2^{ABa}	10.7 ± 6.1^{Aa}	17.0 ± 4.9^{ABa}
S. cordatum	13.8 ± 3.8^{Ca}	9.4 ± 1.7^{Ba}	7.1 ± 1.0^{ABa}	6.5 ± 0.9^{ABa}	5.0 ± 1.1^{Aa}	8.7 ± 2.0^{Ba}
M. undata	18.2 ± 6.2^{Ca}	17.9 ± 7.7^{Ca}	13.7 ± 5.8^{ABCa}	8.7 ± 2.4^{ABa}	6.6 ± 1.4^{Aa}	14.5 ± 6.5^{BCa}
C. dependens	14.9 ± 5.8^{Ea}	11.7 ± 4.9^{Da}	8.5 ± 3.9^{Ca}	6.8 ± 2.6^{Ba}	5.1 ± 1.5^{Aa}	10.2 ± 2.5^{Da}

Results expressed as Means ± SD. Values along time points followed by similar upper case letters and values across extracts followed by similar lower case superscript are not statistically different at $p \leq 0.05$.

Table 4.11: Effects of intraperitoneal administration of the five aqueous plants extracts at 93.5 mg/kg body weight to alloxan induced diabetic mice on blood glucose levels

Extract	0hr	2hr	4hr	6hr	8hr	24hr
P. capensis	16.2 ± 5.1^{Db}	12.5 ± 4.7^{DCc}	10.4 ± 3.7^{ABCb}	7.9 ± 2.4^{ABb}	6.8 ± 2.1^{Ac}	10.6 ± 2.0^{CDb}
M. subcordata	13.0 ± 2.0^{Cab}	10.4 ± 2.6^{BCbc}	9.1 ± 1.4^{ABb}	7.8 ± 0.8^{Ab}	6.3 ± 1.0^{Abc}	9.6 ± 1.5^{ABCb}
S. cordatum	10.9 ± 1.4^{Ca}	4.1 ± 1.1^{Ba}	3.7 ± 0.7^{ABa}	2.9 ± 0.5^{Aa}	3.2 ± 0.4^{ABa}	11.0 ± 0.6^{Cb}
M. undata	11.0 ± 0.6^{Da}	5.6 ± 2.0^{BCab}	4.4 ± 0.6^{ABa}	3.8 ± 0.4^{Aa}	3.4 ± 0.5^{Aa}	6.2 ± 0.7^{Ca}
C. dependens	12.8 ± 1.1^{Bab}	5.4 ± 1.1^{Aab}	4.5 ± 0.7^{Aa}	4.2 ± 0.7^{Aa}	4.3 ± 1.2^{Aab}	4.0 ± 0.9^{Aa}

Results expressed as Means ± SD. Values along time points followed by similar upper case letters and values across extracts followed by similar lower case superscript are not statistically different at $p \leq 0.05$.

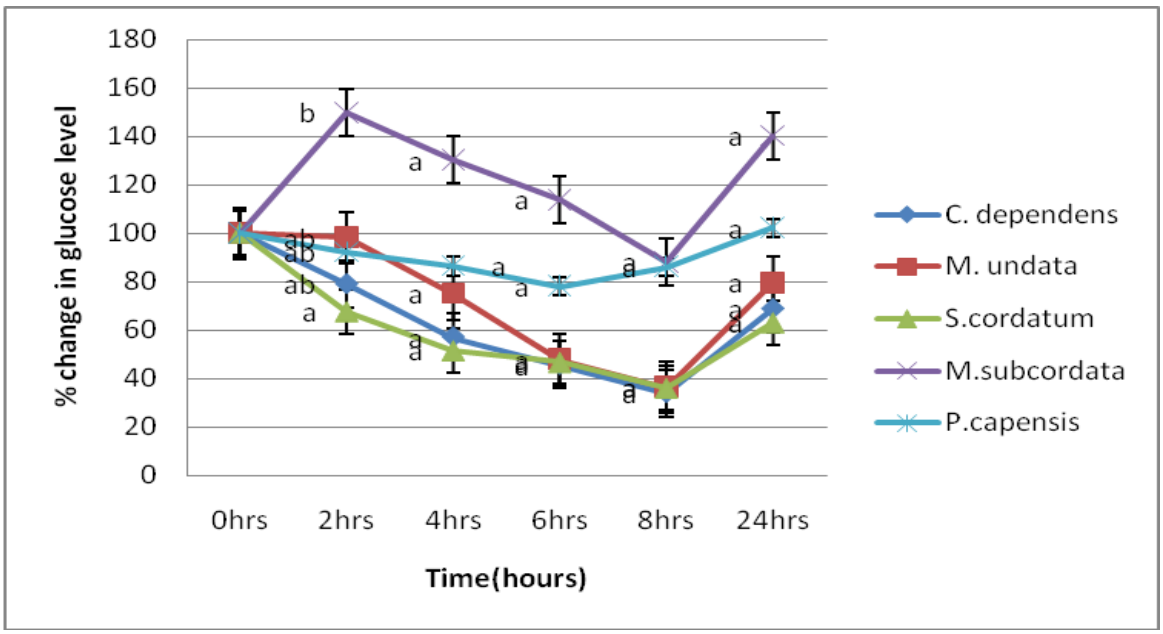

Figure 4.15: Percentage change in blood glucose levels after oral administration of the five aqueous plants extracts at 93.5 mg/kg body weight to alloxan induced diabetic mice. Values at different time points with similar superscript are not significantly different at $p \leq 0.05$.

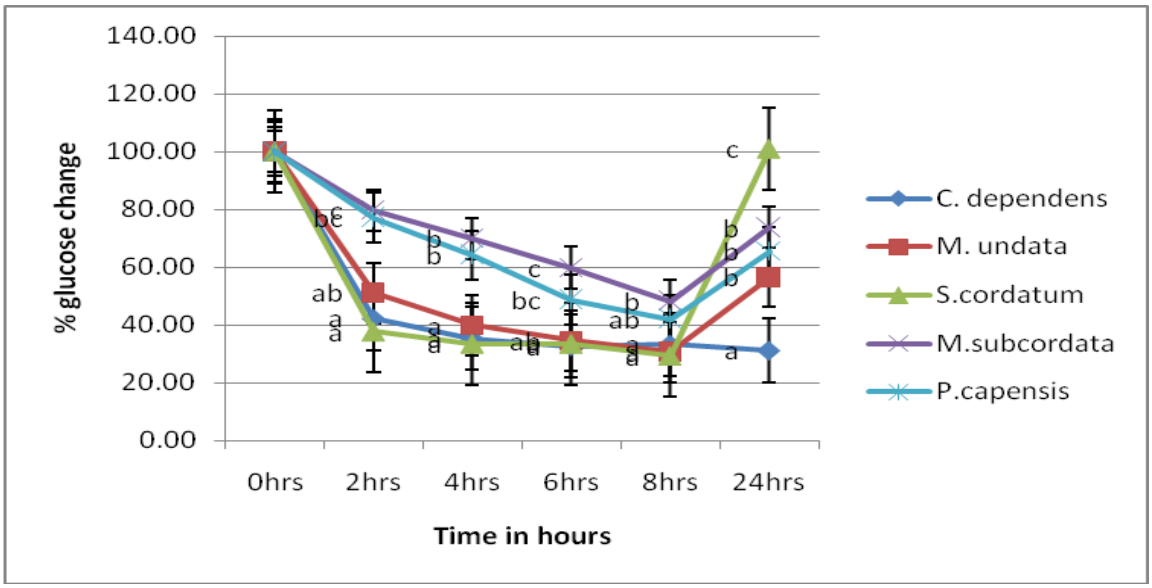

Figure 4.16: Percentage change in blood glucose levels after intraperitoneal administration of the five aqueous plants extracts at 93.5 mg/kg body weight to alloxan induced diabetic mice. Values at different time points with similar superscript are not significantly different at $p \leq 0.05$.

4.2.4 Effects of oral and intraperitoneal administration of the five aqueous plants extracts at 180.9 mg/kg body weight to alloxan induced diabetic mice on blood glucose levels

Oral administration of aqueous extracts of *C. dependens*, *M. undata*, *S. cordatum*, and *P. capensis* to alloxan induced diabetic mice at 180.9 mg/kg body weight in the second hour reduced blood glucose to 79.4, 86.4, 82.5 and 87.3 %, respectively, while aqueous extracts of *M. subcordata* raised blood glucose levels to 107.6 %. Four hours later, oral administration of aqueous extracts of *C. dependens*, *M. undata*, *S. cordatum*, *M. subcordata* and *P. capensis* to alloxan induced diabetic mice at 180.9 mg/kg body weight reduced the blood glucose level to 64.7, 75.3, 58.8, 91.2 and 90.0 %, respectively. There was no significant difference in the effects of oral administration of aqueous extracts of *C. dependens, M.undata* and *S. cordatum* to alloxan induced diabetic mice on blood glucose at the eighth hour ($\rho > 0.05$) where levels were reduced to 41.2, 38.3 and 37.1 %, respectively. In the twenty-fourth hour oral administration of aqueous extracts of *C. dependens, M. undata, S. cordatum,* and *P.capensis* to alloxan induced diabetic mice reduced blood glucose levels to 64, 72.1, 66.5, 67.3 %, respectively, whereas oral administered of aqueous extracts of *M. subcordata* to alloxan induced diabetic mice reverted back to their diabetic state (Table 4.12; Figure 4.17).

Intraperitoneal administration of aqueous extracts of *C. dependens, M. undata, S. cordatum, M. subcordata* and *P.capensis* to alloxan induced diabetic mice at a dose of 180.9 mg/kg body weight lowered blood glucose levels in the second hour to 56, 53.7, 83.3, 82.2, and 72.0 %, respectively. Four hours after intraperitoneal administration of the aqueous extracts to alloxan induced diabetic mice blood glucose levels reduced to

33.6, 43.5, 60.8, 75.2 and 51.1 %, respectively. Eight hours later, intraperitoneal administration of aqueous extracts of *C. dependens, M. undata*, *S. cordatum*, *M. subcordata* and *P. capensis* to alloxan induced diabetic mice reduced glucose levels to 29.6, 36.1, 40.2, 47.8 and 37.1 %, respectively. There was no significant difference in glucose levels after intraperitoneal administration of aqueous extracts of *C. dependens* and *M. undata* to alloxan induced diabetic mice at the second, fourth and sixth hour ($\rho > 0.05$). Twenty four hours later, intraperitoneal administration of aqueous extracts of *C. dependens, M. undata*, *S. cordatum, M. subcordata* and *P. capensis* to alloxan induced diabetic mice reduced blood glucose to 26.4, 60.2, 68.1, 73.9 and 65.7 %, respectively. The results show that intraperitoneal administration of aqueous extracts of *C. dependens* to alloxan induced diabetic mice reduced blood glucose to levels which were significantly higher than those of the other four extracts (Table 4.13; Figure 4.18).

Table 4.12: Effects of oral administration of the five aqueous plants extracts at 180.9 mg/kg body weight to alloxan induced diabetic mice on blood glucose levels

Extract	0hrs	2hrs	4hrs	6hrs	8hrs	24hrs
P. capensis	11.0 ± 2.7^{Ba}	9.6 ± 1.8^{BCa}	9.9 ± 3.0^{BCa}	8.1 ± 1.9^{BCa}	7.5 ± 1.7^{Aa}	7.4 ± 1.8^{Aa}
M. subcordata	15.9 ± 4.1^{Ca}	17.1 ± 7.1^{BCa}	14.5 ± 7.4^{BCa}	13.1 ± 7.4^{ABa}	9.9 ± 5.3^{Aa}	17.1 ± 4.1^{BCb}
S. cordatum	19.4 ± 7.2^{Da}	16.0 ± 7.7^{Ca}	11.4 ± 5.9^{ABa}	9.0 ± 4.6^{Aa}	7.2 ± 2.9^{Aa}	12.9 ± 4.3^{BCab}
M. undata	15.4 ± 4.0^{Aa}	13.3 ± 8.2^{Aa}	11.6 ± 7.6^{Aa}	10.3 ± 7.5^{Aa}	5.9 ± 1.3^{Aa}	11.1 ± 3.7^{Aa}
C. dependens	13.6 ± 3.3^{Da}	10.8 ± 2.3^{Ca}	8.8 ± 1.5^{BCa}	7.4 ± 0.7^{ABa}	5.6 ± 1.2^{Aa}	8.7 ± 1.8^{ABa}

Results expressed as Means ± SD. Values along time points followed by similar upper case letters and values across extracts followed by similar lower case superscript are not statistically different at $p \leq 0.05$.

Table 4.13: Effects of intraperitoneal administration of the five aqueous plants extracts at 180.9 mg/kg body weight to alloxan induced diabetic mice on blood glucose levels

Extract	0hrs	2hrs	4hrs	6hrs	8hrs	24hrs
P. capensis	14.3 ± 3.1^{Dab}	10.3 ± 2.7^{Cab}	7.3 ± 2.7^{ABabc}	6.1 ± 2.4^{Aab}	5.3 ± 2.1^{Aab}	9.4 ± 2.0^{BCbc}
M. subcordata	15.7 ± 3.0^{Dab}	12.9 ± 3.2^{Cab}	11.8 ± 3.1^{BCbc}	9.4 ± 3.2^{ABab}	7.5 ± 1.4^{Aab}	11.6 ± 1.6^{BCbc}
S. cordatum	20.4 ± 4.3^{Db}	17.0 ± 4.6^{Cb}	12.4 ± 3.6^{ABc}	9.6 ± 2.7^{Ab}	8.2 ± 2.1^{Ab}	13.9 ± 3.7^{CDc}
M. undata	10.8 ± 1.2^{Da}	5.8 ± 1.7^{BCa}	4.7 ± 1.1^{ABab}	4.3 ± 0.8^{Aab}	3.9 ± 1.0^{Aa}	6.5 ± 0.8^{Cab}
C. dependens	12.5 ± 3.5^{Bab}	7.0 ± 6.3^{Aa}	4.2 ± 1.0^{Aa}	3.8 ± 0.9^{Aa}	3.7 ± 1.2^{Aa}	3.3 ± 1.0^{Aa}

Results expressed as Means ± SD. Values along time points followed by similar upper case letters and values across extracts followed by similar lower case superscript are not statistically different at $p \leq 0.05$.

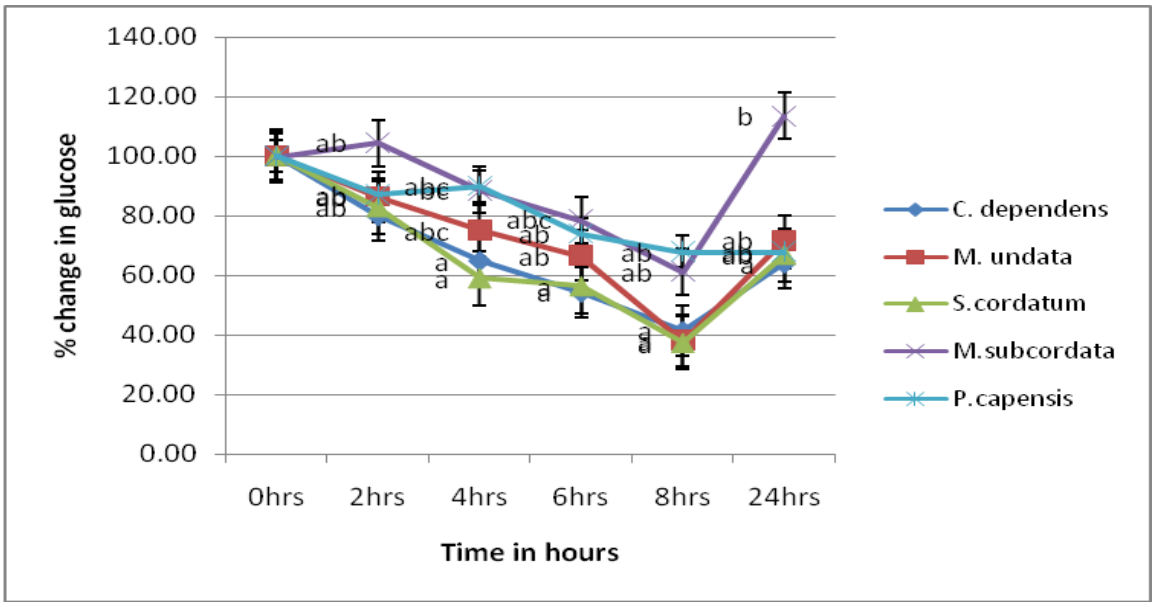

Figure 4.17: Percentage change in blood glucose levels after oral administration of the five aqueous plants extracts at 180.9 mg/kg body weight to alloxan induced diabetic mice. Values at different time points with similar superscript are not significantly different at $p \leq 0.05$.

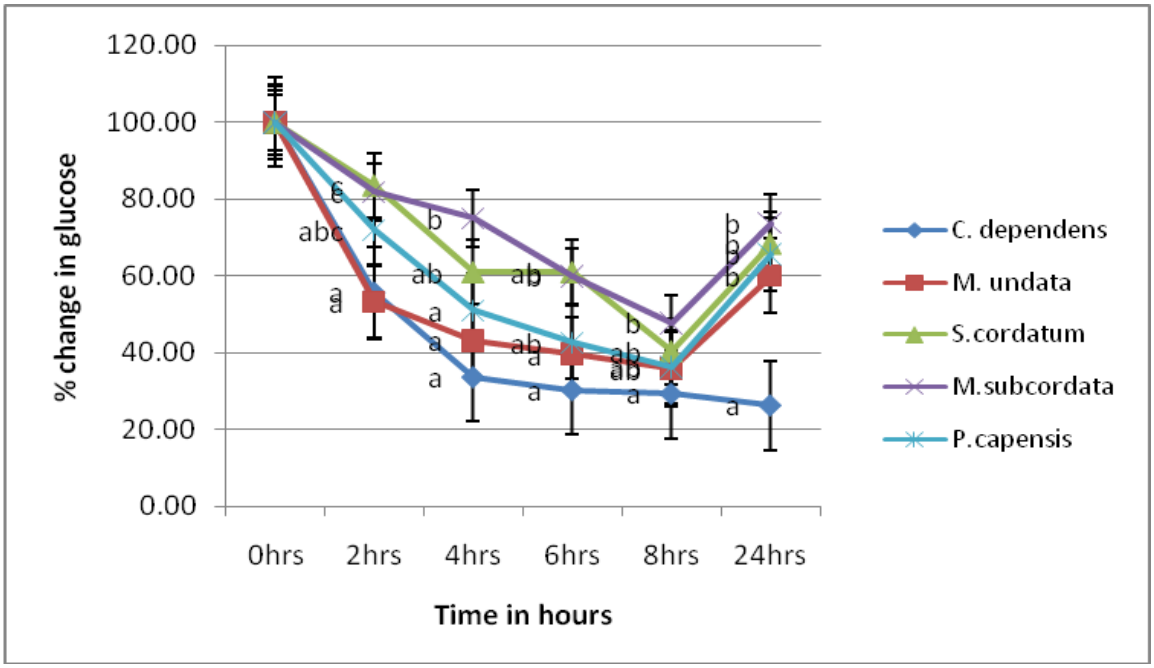

Figure 4.18: Percentage change in blood glucose levels after intraperitoneal administration of the five aqueous plants extracts at 180.9 mg/kg body weight to alloxan induced diabetic mice. Values at different time points with similar superscript are not significantly different at $p \leq 0.05$.

4.2.5 Effects of oral and intraperitoneal administration of the five aqueous plants extracts at 350 mg/kg body weight to alloxan induced diabetic mice on blood glucose levels

In the oral route, the effects of plant extracts increased gradually with time and resolved by the twenty-fourth hour. In the second hour, aqueous extracts of *C.dependens, M. undata, S. cordatum, M. subcordata* and *P. capensis* to alloxan induced diabetic mice reduced blood glucose levels to 69.8, 58.8, 73.6, 76.3 and 59.5 %, respectively. Six hours later, the same aqueous extracts reduced glucose to 53.8, 45.9, 60.0, 80.4 and 61.1 %, respectively. In the eight hour blood glucose levels in alloxan induced diabetic mice orally administered with aqueous extracts of *C. dependens, M.undata, S. cordatum, M. subcordata* and *P.capensis* reduced to 36.1, 31.8, 53.6, 66.2 and 78.6 %, respectively. At twenty-fourth hour, aqueous extracts of *C. dependens, M. undata , S. cordatum, M. subcordata* and *P. capensis* reduced blood glucose by 58.6, 77.1, 67.9, 83.8 and 81.3 %, respectively. There was no significant difference in blood glucose levels for the five extracts at the second, fourth, sixth and twenty-fourth hour for this dose ($\rho > 0.05$) and the most effective extract was *M. undata* (Table 4.14; Figure 4.19).

Intraperitoneal administration of aqueous extracts at the same dose to alloxan induced diabetic mice appreciably reduced blood glucose levels over a period of twenty-four hours. In the second hour, intraperitoneal administration of aqueous extracts of *C. dependens, M. undata, S. cordatum, M. subcordata,* and *P.capensis* to alloxan induced diabetic mice reduced blood glucose levels to 40.3, 50.8, 42.8, 70.1 and 68.9 %, respectively. Four hours later, the intraperitoneal administration of aqueous extracts to alloxan induced diabetic mice reduced glucose levels to 30.9, 37.9, 39.5, 56.9 and 50 %,

respectively. In the eighth hour, intraperitoneal administration of aqueous extracts of *C. dependens, M. undata, S. cordatum, M. subcordata* and *P. capensis* to alloxan induced diabetic mice lowered blood glucose levels to 30.2, 34.7, 23, 50.7 and 33.1%, respectively, in the same order. In the twenty-fourth hour, intraperitoneal administration of the plant extracts of *C. dependens, M. undata, S. cordatum, M. subcordata* and *P. capensis* to alloxan induced diabetic mice reduced glucose levels to 25.9, 46.0, 81.6, 81.2 and 57.4 %, respectively. There was no significant variation in blood glucose levels after intraperitoneal administration of *C. dependens* and *S. cordatum* to alloxan induced diabetic mice at the eighth hour, and C. *dependens* and *M. undata* to alloxan induced diabetic mice at the twenty-fourth hour ($p > 0.05$), (Table 4:15; Figure 4:20).

Table 4.14: Comparison of hypoglycemic effects after oral administration of the five aqueous plants extracts at 350 mg/kg body weight to alloxan induced diabetic mice

Extract	0hrs	2hrs	4hrs	6hrs	8hrs	24hrs
P. capensis	14.4 ± 4.7^{Aa}	10.1 ± 2.1^{Aa}	8.2 ± 1.8^{Aa}	8.3 ± 4.6^{Aa}	7.3 ± 3.3^{Aa}	11.7 ± 9.6^{Aa}
M. subcordata	14.8 ± 4.1^{Aa}	12.3 ± 3.2^{Aa}	11.3 ± 3.9^{Aa}	11.9 ± 5.1^{Aa}	9.8 ± 4.3^{Aa}	12.4 ± 5.2^{Aa}
S. cordatum	14.0 ± 4.5^{Da}	12.3 ± 4.1^{BCa}	10.3 ± 3.0^{ABCa}	8.4 ± 2.1^{ABa}	7.5 ± 2.0^{Aa}	9.5 ± 1.8^{ABa}
M. undata	17.0 ± 6.7^{Ca}	12.2 ± 5.4^{ABCa}	10.0 ± 4.8^{ABa}	7.8 ± 1.6^{ABa}	5.4 ± 2.9^{Aa}	13.1 ± 7.5^{BCa}
C. dependens	16.9 ± 4.1^{Da}	14.2 ± 2.9^{CDa}	11.8 ± 2.3^{BCa}	9.1 ± 3.5^{ABa}	6.1 ± 1.4^{Aa}	9.9 ± 1.9^{ABa}

Results expressed as Means ± SD. Values along time points followed by similar upper case letters and values across extracts followed by similar lower case superscript are not statistically different at $p \leq 0.05$.

Table 4.15: Comparison of hypoglycemic effects after intraperitoneal administration of the five aqueous plant extracts at 350 mg/kg body weight to alloxan induced diabetic mice

Extract	0hrs	2hrs	4hrs	6hrs	8hrs	24hrs
P. capensis	14.8 ± 4.4^{Da}	10.2 ± 3.5^{Ca}	7.4 ± 2.0^{ABCa}	5.5 ± 0.8^{ABab}	4.9 ± 0.8^{Aa}	8.5 ± 0.9^{BCd}
M. subcordata	14.4 ± 3.0^{Ca}	10.1 ± 2.5^{ABCa}	8.2 ± 1.6^{ABa}	8.3 ± 2.9^{ABb}	7.3 ± 1.2^{Ab}	11.7 ± 1.6^{BCb}
S. cordatum	15.2 ± 8.1^{Ba}	6.5 ± 4.7^{Aa}	6.0 ± 4.6^{Aa}	5.1 ± 4.0^{Aab}	3.5 ± 0.5^{Aa}	12.4 ± 2.7^{Bbc}
M. undata	12.4 ± 2.7^{Ba}	6.3 ± 1.9^{Aa}	4.7 ± 1.5^{Aa}	4.6 ± 1.5^{Aab}	4.3 ± 1.0^{Aa}	5.7 ± 1.2^{Aa}
C. dependens	13.9 ± 2.6^{Ba}	5.6 ± 2.5^{Aa}	4.3 ± 2.3^{Aa}	3.8 ± 1.1^{Aa}	4.2 ± 2.1^{Aa}	3.6 ± 1.9^{Aa}

Results expressed as Means ± SD. Values along time points followed by similar upper case letters and values across extracts followed by similar lower case superscript are not statistically different at $p \leq 0.05$.

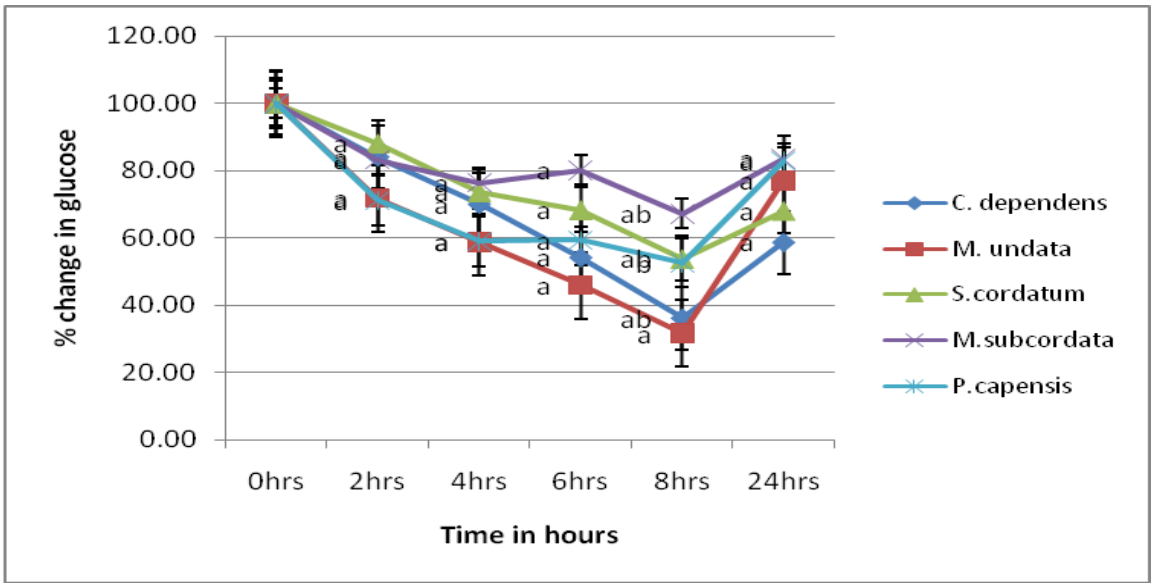

Figure 4.19: Percentage change in blood glucose levels after oral administration of the five aqueous plants extracts at 350 mg/kg body weight to alloxan induced diabetic mice. Values at different time points with similar superscript are not significantly different at $p \leq 0.05$.

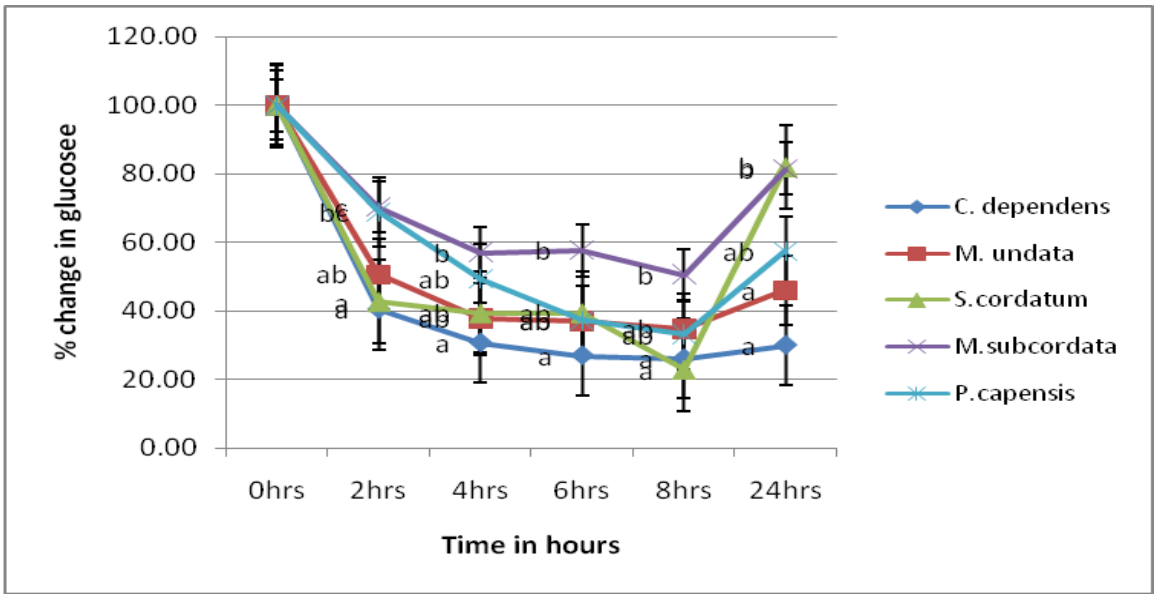

Figure 4.20: Percentage change in blood glucose levels after intraperitoneal administration of the five aqueous plants extracts at 350 mg/kg body weight to alloxan induced diabetic mice. Values at different time points with similar superscript are not significantly different at $p \leq 0.05$.

4.3 Effects of a daily oral and intraperitoneal administration of the five aqueous extracts at high doses to mice for 28 days on body weight and average weekly body weight change

The toxicity effects of aqueous plant extracts at high doses of 450, 670 and 1000 mg/kg body weight was evaluated by assessing the average weekly body weight changes in mice, relative percent organ to body weight, hematological and biochemical parameters. In addition, histopathological changes were also evaluated in the cell structure of the studied organs.

4.3.1 Effects of orally and intraperitoneally administered aqueous plant extracts of *C. dependens* and *M. undata* to mice daily for 28 days at high doses on body weights and average weekly body weight change

Tables 4.16-4.17 shows the effects of oral and intraperitoneal administration of aqueous extracts of *C. dependens* to mice daily for 28 days on weekly body weight changes and the average weekly body weights change. The results indicate that oral administration of aqueous extracts of *C. dependens* to mice daily for 28 days at 450, 670, and 1000 mg/kg body weight caused a significant reduction in both the body weight gain and average weekly weight gain relative to the normal control mice group ($\rho < 0.05$). The extract-treated mice groups at 450, 670, and 1000 mg/kg body weight caused a similar body weight gain and average weekly weight gain ($\rho > 0.05$). Further, intraperitoneal administration of aqueous extracts of *C. dependens* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight caused a significant reduction in both the body weight gain and the average weekly weight gain relative to the normal control mice group ($\rho < 0.05$). The extract-treated mice group at 450, and 670 mg/kg body weight caused a similar body weight gain and average weekly weight gain ($\rho > 0.05$). Further, the

extract-treated mice groups at 670 and 1000 mg/kg body weight caused a similar body weight gain and average weekly weight gain ($\rho > 0.05$).

Table 4.16: Effects of oral administration of aqueous extracts of *C. dependens* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight on the body weight and average weekly body weight

Treatment (mg/kgbwt)	Weekly change in weight					
	0	1	2	3	4	Δ weight (g/week)
Control(Oral)	20.2 ± 0.5^{a}	22.2 ± 0.4^{a}	24.0 ± 0.5^{b}	26.0 ± 0.4^{b}	28.4 ± 0.6^{b}	2.1 ± 0.1^{b}
450	23.6 ± 1.7^{b}	24.4 ± 1.7^{a}	25.3 ± 1.8^{bc}	26.5 ± 1.8^{b}	27.3 ± 1.6^{a}	0.9 ± 0.0^{a}
670	24.8 ± 0.5^{b}	25.5 ± 0.5^{a}	26.6 ± 0.5^{c}	27.4 ± 0.4^{b}	28.0 ± 0.4^{ab}	0.8 ± 0.1^{a}
1000	20.2 ± 0.5^{a}	20.7 ± 0.6^{a}	21.5 ± 0.7^{a}	23.0 ± 0.5^{a}	23.2 ± 0.8^{a}	0.8 ± 0.2^{a}

Results expressed as Mean ± SD for five animals per group. Values with the same superscript in different doses are not significantly different from each other at $p \leq 0.05$ using ANOVA and post ANOVA statistical analysis.

Table 4.17: Effects of intraperitoneal administration of aqueous extracts of *C. dependens* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight on the body weight and average weekly body weight

Treatment (mg/kgbwt)	Weekly change in weight					
	0	1	2	3	4	Δ weight (g/week)
Control (IP)	20.6 ± 0.9^{a}	22.7 ± 0.9^{a}	24.9 ± 0.9^{a}	26.8 ± 0.8^{a}	29.0 ± 0.7^{b}	2.1 ± 0.0^{c}
450	21.8 ± 2.2^{ab}	22.6 ± 2.2^{a}	23.6 ± 2.0^{a}	24.7 ± 2.1^{a}	25.5 ± 2.1^{a}	0.9 ± 0.1^{b}
670	24.0 ± 1.7^{b}	25.0 ± 1.6^{a}	26.0 ± 1.63^{a}	27.0 ± 1.9^{a}	27.0 ± 2.0^{ab}	0.8 ± 0.1^{ab}
1000	22.4 ± 0.6^{ab}	23.0 ± 0.5^{a}	23.9 ± 0.5^{a}	24.8 ± 0.5^{a}	25.2 ± 0.5^{a}	0.7 ± 0.0^{a}

Results expressed as Mean ± SD for five animals per group. Values with the same superscript in different doses are not significantly different from each other at $p \leq 0.05$ using ANOVA and post ANOVA statistical analysis.

Table 4.18 and 4.19 depicts the effects of oral and intraperitoneal administration of aqueous extracts of *M. undata* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight on the body weight gain and average weekly weight gain. Results indicate that oral administration of aqueous extracts of *M. undata* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight caused a significant dose independent reduction in body weight gain and average weekly body weight gain relative to the normal control mice group ($\rho < 0.05$). The extract-treated mice groups at 450 and 670 mg/kg body weight caused a similar reduction in weight gain ($\rho < 0.05$) which was significantly higher than that of the extract-treated mice at 1000 mg/kg body weight dose ($\rho < 0.05$). The extract-treated mice group at 1000 mg/kg body weight caused the greatest reduction in body weight gain relative to the normal control mice group. Interestingly, the extract-treated mice group at 670 and 1000 mg/kg body weight caused a similar reduction in the average weekly weight gain ($\rho > 0.05$) which was significantly higher than the extract-treated mice group at 450 mg/kg body weight dose ($\rho < 0.05$).

Intraperitoneal administration of aqueous extracts of *M. undata* to mice daily for 28 days at 450, 670, and 1000 mg/kg body weight caused a significant dose dependent reduction in both the body weight gain and average weekly body weight gain relative to that of the normal control mice group ($\rho < 0.05$). The extract-treated mice groups at 450, 670, and 1000 mg/kg body caused a significant dose dependent decrease in both the body weight gain and average weekly body weight gain with the 450 mg/kg body weight dose causing the greatest reduction in the two measured parameters ($\rho < 0.05$). The extract-treated mice group at 450 mg/kg body weight caused the greatest reduction

in the body weight gain and average weekly body weight gain relative to that of the normal control mice group ($\rho < 0.05$).

Table 4.18: Effects of oral administration of aqueous extracts of *M. undata* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight on the body weight and average weekly body weight

Treatment (mg/kgbwt)	Weekly change in weight					
	0	1	2	3	4	Δ weight (g/week)
Control (Oral)	20.2 ± 0.5^{a}	22.2 ± 0.4^{a}	24.0 ± 0.5^{b}	26.0 ± 0.4^{b}	28.4 ± 0.6^{b}	2.1 ± 0.1^{c}
450	21.4 ± 2.4^{a}	22.3 ± 2.3^{a}	23.1 ± 2.3^{a}	23.8 ± 2.3^{a}	24.6 ± 2.2^{a}	0.5 ± 0.0^{a}
670	22.0 ± 1.0^{a}	23.1 ± 1.1^{a}	23.9 ± 1.0^{ab}	24.3 ± 1.1^{a}	25.1 ± 1.1^{a}	0.8 ± 0.0^{b}
1000	23.4 ± 1.1^{a}	23.9 ± 1.2^{a}	24.4 ± 1.3^{ab}	24.9 ± 1.3^{a}	25.3 ± 1.2^{a}	0.8 ± 0.0^{b}

Results expressed as Mean ± SD for five animals per group. Values with the same superscript in different doses are not significantly different from each other at $p \leq 0.05$ using ANOVA and post ANOVA statistical analysis.

Table 4.19: Effects of intraperitoneal administration of aqueous extracts of *M. undata* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight on the body weight and average weekly body weight

Treatment (mg/kgbwt)	Weekly change in weight					
	0	1	2	3	4	Δ weight (g/week)
Control (IP)	20.6 ± 0.9^{a}	22.7 ± 0.9^{a}	24.9 ± 0.9^{a}	26.8 ± 0.8^{a}	29.0 ± 0.7^{b}	2.1 ± 0.1^{d}
450	21.8 ± 2.2^{ab}	22.7 ± 2.2^{a}	23.5 ± 2.2^{a}	24.3 ± 2.2^{a}	25.1 ± 2.2^{a}	0.8 ± 0.0^{c}
670	23 ± 1.6^{ab}	23.7 ± 1.5^{a}	24.3 ± 1.5^{a}	24.8 ± 1.4^{a}	25.4 ± 1.5^{a}	0.6 ± 0.0^{b}
1000	23.6 ± 1.1^{b}	24.1±1.3a	24.4 ± 1.2^{a}	24.8 ± 1.2^{a}	25.3 ± 1.2^{a}	0.4 ± 0.0^{a}

Results expressed as Mean ± SD for five animals per group. Values with the same superscript in different doses are not significantly different from each other at $p \leq 0.05$ using ANOVA and post ANOVA statistical analysis.

4.3.2 Effects of oral and intraperitoneal administration of aqueous extracts of *S. cordatum*, *M. subcordata* and *P. capensis* to mice daily for 28 days at high doses on the body weight and average weekly body weight

Table 4.20-4.21 show the effects of a daily oral and intraperitoneal administration of aqueous extracts of *S. cordatum* to mice for 28 days at 450, 670 and 1000 mg/kg body weight on body weight and average weekly body weight. Results show that a daily oral and intraperitoneal administration of aqueous extracts of *S. cordatum* to mice for 28 days at 450, 670 and 1000 mg/kg body weight caused a significant dose dependent reduction in both the body weight and average weekly body weight relative to the normal control mice group. The extract-treated mice groups caused a significant dose dependent reduction in both the body weight and average weekly body weight with the 1000 mg/kg body weight dose giving the greatest reduction of the two measured parameters.

Table 4.20: Effects of a daily oral administration of aqueous extracts of *S. cordutum* to mice for 28 days at 450, 670 and 1000 mg/kg body weight on the body weight and the average weekly body weight

Treatment (mg/kgbwt)	Weekly change in weight					
	0	1	2	3	4	Δ weight (g/week)
Control (Oral)	20.2±0.5^{a}	22.2±0.4^{a}	24.0±0.5^{a}	26.0±0.4^{c}	28.4±0.6^{b}	2.1±0.1^{c}
450	21.4±1.7a	22.9±1.6^{a}	24.1±1.7^{a}	25.4±1.7^{bc}	26.7±1.7^{ab}	1.3±0.1^{b}
670	20.4±1.7a	21.4±1.6^{a}	22.6±1.7^{a}	23.4±1.7^{ab}	24.2±1.7^{a}	1.0±0.0^{ab}
1000	21.2±1.1a	21.7±1.2^{a}	22.2±1.2^{a}	22.6±1.2^{a}	24.0±2.3^{a}	0.5±.0.2^{a}

Results expressed as Mean ± SD for five animals per group. Values with the same superscript in different doses are not significantly different from each other at $p \leq 0.05$ using ANOVA and post ANOVA statistical analysis.

Table 4.21: Effects of a daily intraperitoneal administration of aqueous extracts of *S. cordutum* to mice for 28 days at 450, 670 and 1000 mg/kg body weight on the body weight and the average weekly body weight

Treatment (mg/kgbwt)	Weekly change in weight					
	0	1	2	3	4	Δ weight (g/week)
Control (IP)	20.6±0.9a	22.7±0.9^{a}	24.9±0.9^{b}	26.8±0.8^{c}	29.0±0.7^{b}	2.1±0.1^{d}
450	21.2±2.2a	22.6±2.1^{a}	23.9±2.2^{ab}	25.2±2.1^{bc}	26.5±2.1^{b}	1.3±0.1^{c}
670	20.6±1.1a	21.3±1.0^{a}	22.1±1.1^{a}	22.9±1.1^{ab}	23.6±1.0^{a}	0.8±0.1^{b}
1000	20.4±1.5a	20.8±1.5^{a}	21.3±1.5^{a}	21.8±1.5^{a}	22.2±1.5^{a}	0.5±0.0^{a}

Results expressed as Mean ± SD for five animals per group. Values with the same superscript in different doses are not significantly different from each other at $p \leq 0.05$ using ANOVA and post ANOVA statistical analysis.

Table 4.22-4.23 show the effects of a daily oral and intraperitoneal administration of aqueous extracts of *M. subcordata* to mice for 28 days at 450, 670 and 1000 mg/kg body weight on body weight and average weekly body weight. Results show that a daily oral administration of aqueous extracts of *M. subcordata* to mice for 28 days at 450, 670 and 1000 mg/kg body weight caused a significant dose independent reduction in both the body weight and average weekly body weight relative to the normal control mice group ($\rho < 0.05$). The extract-treated mice groups at the three tested extract doses caused a similar reduction of both the body weight and the average weekly body weight ($\rho > 0.05$). Results show that a daily intraperitoneal administration of aqueous extracts of *M. subcordata* to mice for 28 days at 450, 670 and 1000 mg/kg body weight caused a significant dose dependent reduction in both the body weight and average weekly body weight relative to the normal control mice group ($\rho < 0.05$). The extract-treated mice groups at 450 and 670 mg/kg body weight caused a similar reduction of both the body weight and the average weekly body weight ($\rho > 0.05$). The extract-treated mice groups at 670 and 1000 mg/kg body weight also caused a similar reduction in both the body weight and the average weekly body weight ($\rho > 0.05$). The extract-treated mice at 1000 mg/kg body weight caused the greatest reduction in both the body weight and the average weekly body weight relative to the normal control mice group ($\rho < 0.05$).

Table 4.22: Effects of a daily oral administration of aqueous extracts of *M. subcordata* to mice for 28 days at 450, 670 and 1000 mg/kg body weight on the body weight and average weekly body weight

Treatment (mg/kgbwt)	Weekly change in weight					Δ weight (g/week)
	0	1	2	3	4	
Control (Oral)	22.8±1.9^{a}	24.7±1.9^{a}	26.4±1.8^{a}	28.5±1.7^{a}	30.5±1.8^{a}	1.9±0.1^{b}
450	24.6±1.1^{a}	25.9±1.2^{a}	27.1±1.0^{a}	28.2±1.1^{a}	29.4±0.9^{a}	1.2±0.1^{a}
670	24.0±1.0^{a}	25.3±0.9^{a}	26.4±1.0^{a}	27.4±1.0^{a}	28.3±1.0^{a}	1.1±0.1^{a}
1000	24.2±0.8^{a}	25.6±0.9^{a}	26.5±0.8^{a}	27.5±0.9^{a}	28.6±1.0^{a}	1.1±0.1^{a}

Results expressed as Mean ± SD for five animals per group. Values with the same superscript in different doses are not significantly different from each other at $p \leq 0.05$ using ANOVA and post ANOVA statistical analysis.

Table 4.23: Effects of a daily intraperitoneal administration of aqueous extracts of *M. subcordata* to mice for 28 days at 450, 670 and 1000 mg/kg body weight on the body weight and average weekly body weight

Treatment (mg/kgbwt)	Weekly change in weight					Δ weight (g/week)
	0	1	2	3	4	
Control (IP)	24.2±1.3^{a}	26.2±1.2^{a}	27.9±1.0^{a}	30.0±0.9^{b}	31.9±0.9^{b}	1.9±0.2^{c}
450	24.8±1.1^{a}	26.2±1.2^{a}	27.1±1.5^{a}	28.2±1.0^{ab}	29.4±0.9^{a}	1.2±0.1^{b}
670	24.6±1.1^{a}	25.9±1.1^{a}	27.0±1.1^{a}	28.1±2.0^{ab}	29.0±1.1^{a}	1.1±0.0^{ab}
1000	24.2±1.3^{a}	25.4±1.2^{a}	26.3±1.4^{a}	27.1±1.5^{a}	27.8±1.5^{a}	0.9±0.1^{a}

Results expressed as Mean ± SD for five animals per group. Values with the same superscript in different doses are not significantly different from each other at $p \leq 0.05$ using ANOVA and post ANOVA statistical analysis.

Table 4.24-4.25 show the effects of a daily oral and intraperitoneal administration of aqueous extracts of *P. capensis* to mice for 28 days at 450, 670 and 1000 mg/kg body weight on body weight and the weekly average body weight. Results show that a daily oral and intraperitoneal administration of aqueous extracts of *P. capensis* to mice for 28 days at 450, 670 and 1000 mg/kg body weight caused a significant dose dependent reduction in both the body weight and average weekly body weight relative to the normal control mice group ($\rho < 0.05$). The extract-treated mice groups at 450, 670 and 1000 mg/kg body weight caused a significant dose dependent reduction in both the body weight and average weekly body weight with 1000 mg/kg body weight dose giving the greatest reduction in the two measured parameters for both extract administration routes ($\rho < 0.05$). The extract-treated mice group at 1000 mg/kg body weight caused the greatest reduction in both the body weight and the average weekly body weight relative to the normal control mice group ($\rho < 0.05$).

Table 4.24: Effects of a daily oral administration of aqueous extracts of *P. capensis* to mice for 28 days at 450, 670 and 1000 mg/kg body weight on the body weight and average weekly body weight

Treatment (mg/kgbwt)	Weekly change in weight					
	0	1	2	3	4	Δ weight (g/week)
Control(Oral)	22.8 ± 1.9^{a}	24.7 ± 1.9^{a}	26.4 ± 1.8^{a}	28.5 ± 1.7^{b}	30.5 ± 1.8^{b}	1.9 ± 0.1^{d}
450	22.8 ± 1.3^{a}	24.3 ± 1.2^{a}	26.0 ± 1.1^{a}	27.7 ± 1.1^{b}	29.5 ± 1.1^{b}	1.7 ± 0.1^{c}
670	23.8 ± 1.3^{a}	25.0 ± 1.3^{a}	26.2 ± 1.3^{a}	27.3 ± 1.3^{ab}	28.6 ± 1.2^{b}	1.2 ± 0.1^{b}
1000	22.8 ± 1.3^{a}	23.5 ± 1.2^{a}	24.3 ± 1.3^{a}	24.9 ± 1.3^{a}	25.4 ± 1.5^{a}	0.7 ± 0.1^{a}

Results expressed as Mean ± SD for five animals per group. Values with the same superscript in different doses are not significantly different from each other at $p \leq 0.05$.

Table 4.25: Effects of a daily intraperitoneal administration of aqueous extracts of *P. capensis* to mice for 28 days at 450, 670 and 1000 mg/kg body weight on the body weight and average weekly body weight

Treatment (mg/kgbwt)	Weekly change in weight					
	0	1	2	3	4	Δ weight (g/week)
Control (IP)	24.2 ± 1.3^{a}	26.2 ± 1.2^{a}	27.9 ± 1.0^{b}	30.0 ± 0.9^{b}	31.9 ± 0.9^{c}	1.9 ± 0.2^{d}
450	22.6 ± 1.7^{a}	24.3 ± 1.6^{a}	25.6 ± 1.6^{ab}	27.5 ± 1.8^{ab}	29.1 ± 1.7^{b}	1.6 ± 0.2^{c}
670	23.6 ± 1.1^{a}	24.8 ± 1.1^{a}	25.8 ± 1.2^{ab}	27.0 ± 1.2^{a}	28.2 ± 1.2^{ab}	1.2 ± 0.1^{b}
1000	23.0 ± 1.6^{a}	23.7 ± 1.6^{a}	24.6 ± 1.5^{a}	25.1 ± 1.6^{a}	25.8 ± 1.6^{a}	0.7 ± 0.0^{a}

Results expressed as Mean ± SD for five animals per group. Values with the same superscript in different doses are not significantly different from each other at $p \leq 0.05$.

4.4 Effects of a daily oral and intraperitoneal administration of the five aqueous plant extracts to mice for 28 days at high doses on the relative percent organ to body weight

Table 4.26 shows the effects of a daily oral administration of aqueous extract of *C. dependens, S. cordatum*, *M. undata*, *M. subcordata* and *P. capensis* to mice for 28 days at 450, 670 and 1000 mg/kg body weight on the relative percent organ to body weight. A daily oral administration of aqueous extracts of *C. dependens*, *M. undata* and *S. cordatum* to mice for 28 days at 450, 670 and 1000 mg/kg body weight significantly decreased the relative percent brain to body weight and increased the relative percent liver, lungs, and testes to body weight relative to that of the normal control mice group. Further, a daily oral administration of aqueous extracts of *C. dependens* to mice for 28 days at 450, 670, and 1000 mg/kg body weight caused a non-significant effect on the relative percent kidney, spleen and heart to body weight relative to that of the normal control mice group (Table 4.26).

Similarly, a daily oral administration of aqueous extracts of *M. undata* to mice for 28 days at 450, 670 and 1000 mg/kg body weight only caused a significant decrease in the relative percent brain to body weight and a significant increase in the relative percent lungs to body weight compared to those of the normal control mice ($p > 0.05$). Further, a daily oral administration of aqueous extracts of *M. undata* to mice for 28 days at 450, 670 and 1000 mg/kg body weight caused a non-significant effect on the relative percent liver, kidney, spleen, testes and heart to body weight relative to that of the normal control mice group (Table 4.26).

In addition, a daily oral administration of aqueous extracts of *S. cordutum* to mice for 28 days at 450, 670 and 1000 mg/kg body weight caused a significant decrease in the relative percent brain to body weight at all the three tested extract doses relative to that of the normal control mice group. Extract-treated mice groups at 450 and 670 mg/kg body weight caused a non-significant effect on the relative percent brain to body weight which was significantly lower than that of the extract-treated mice group at 1000 mg/kg body weight (Table 4.26).

A daily oral administration of aqueous extracts of *S. cordutum* to mice for 28 days at 450, 670, and 1000 mg/kg body weight caused a significant increase in the relative percent liver to body weight at 1000 mg/kg body weight relative to that of the normal control mice group. Extract-treated mice groups at 450 and 670 mg/kg body weight caused a similar effect to the relative percent liver to body weight compared to that of the normal control mice group (Table 4.26).

Further, a daily oral administration of aqueous extracts of *S. cordutum* to mice for 28 days at all the three tested extract doses caused a significant decrease in the relative percent kidney to body weight relative to normal control mice group. However, the extract-treated mice groups at 450, 670 and 1000 mg/kg body weight caused a non-significant effect to the relative percent kidney to body weight (Table 4.26).

A daily oral administration of aqueous extracts of *S. cordutum* to mice for 28 days at 450, 670 and 1000 mg/kg body weight caused a significant increase in the relative

percent lungs to body weight compared to that of the control mice group. However, the extract-treated mice groups at 450 and 670 mg/kg body weight caused similar effects to the relative percent lungs to body weight which was significantly lower than that of the extract-treated mice group at 1000mh/kg body weight (Table 4.26).

A daily oral administration of aqueous extracts of *S. cordutum* to mice for 28 days at 450, 670 and 1000 mg/kg body weight caused a significant decrease in the relative percent testes to body weight at 670 mg/kg body weight compared to the normal control mice group. However, the extract-treated mice groups at 450 and 1000 mg/kg body weight caused a relative percent testes to body weight which was similar to that of the normal control mice group (Table 4.26). Further, a daily oral administration of aqueous extracts of *S. cordutum* to mice daily for 28 days at 450, 670, and 1000 mg/kg body weight caused a non-significant effect on the relative percent spleen and heart to body weight relative to that of the normal control mice group (Table 4.26).

A daily oral administration of aqueous extracts of *M. subcordata* to mice for 28 days at 450, 670, and 1000 mg/kg body weight caused a significant decrease in the relative percent spleen to body weight at 450 mg/kg body weight relative to the normal control mice group. Extract-treated mice groups at 670 and 1000 mg/kg body weight caused a similar effect to the relative percent spleen to body weight which was similar to that of the normal control mice group. Further, a daily oral administration of aqueous extracts of *M. subcordata* to mice daily for 28 days at 450, 670, and 1000 mg/kg body weight

caused a non-significant effect on the relative percent brain, liver, kidney, lungs, testes and heart to body weight relative to that of the normal control mice group (Table 4.26).

A daily oral administration of aqueous extracts of *P. capensis* to mice for 28 days at 450, 670 and 1000 mg/kg body weight caused similar effects to the relative percent brain, kidney, spleen, and testes to body weight at 450 and 670 mg/kg body weight which was similar to that of the normal control mice group. Extract-treated mice group at 1000 mg/kg body weight caused the greatest relative percent brain, kidney, spleen and testes to body weight relative to the normal control mice group. Further, oral administration of aqueous extracts of *P. capensis* to mice daily for 28 days at 450, 670, and 1000 mg/kg body weight caused a non-significant effect on the relative percent liver, lungs and heart to body weight relative to that of the normal control mice group (Table 4.26).

Table 4.26: Effects of a daily oral administration of the five aqueous plants extracts at 450, 670 and 1000 mg/kg body weight to mice for 28 days on the relative percent organ to body weight

Treatment	Relative percent organ to body weight (g/100g)						
	Brain	Liver	Kidney	Lung	Spleen	Testes	Heart
Chasmanthera dependens (mg/kg body weight)							
Control	2.5±0.1^{b}	5.5±0.3^{a}	1.7±0.1^{a}	1.1±0.0^{a}	0.9±0.0^{a}	0.8±0.0^{a}	0.4±0.0^{a}
450	1.9±0.7^{a}	7.4±2.0^{b}	1.7±0.5^{a}	2.4±0.9^{c}	0.9±0.3^{a}	1.0±0.3^{b}	0.5±0.2^{a}
670	1.8±0.7^{a}	8.1±2.2^{b}	1.5±0.5^{a}	2.4±0.9^{c}	0.7±0.3^{a}	0.7±0.3^{ab}	0.4±0.2^{a}
1000	2.5±0.7^{b}	8.0±2.2^{b}	2.0±0.5^{a}	2.1±0.8^{ab}	1.2±0.3^{a}	0.9±0.3^{a}	0.5±0.1^{a}
Mayrtenus undata (mg/kg body weight)							
Control	2.5±0.1^{b}	5.5±0.3^{a}	1.7±0.1^{a}	1.1±0.0a	0.9±0.0^{a}	0.8±0.0^{a}	0.4±0.0^{a}
450	1.3±0.8^{a}	5.0±1.5^{a}	1.2±0.5^{a}	1.5±0.4^{ab}	0.7±0.3^{a}	0.8±0.2^{a}	0.4±0.1^{a}
670	1.1±0.7^{a}	4.3±1.6^{a}	1.3±0.4^{a}	1.1±0.5^{ab}	0.7±0.3^{a}	0.6±0.2^{a}	0.5±0.2^{a}
1000	1.2±0.6^{a}	5.3±1.6^{a}	1.3±0.4^{a}	1.2±0.5^{b}	0.7±0.3^{a}	0.6±0.2^{a}	0.5±0.1^{a}
Syzigium cordutum (mg/kg body weight)							
Control	2.5±0.1^{c}	5.5±0.0^{a}	1.7±0.10^{b}	1.1±0.01^{a}	0.9±0.0^{a}	0.8±0.0^{bc}	0.4±0.0^{a}
450	1.5±0.8^{a}	5.7±1.6^{a}	1.4±0.5^{a}	1.5±0.4^{b}	1.0±0.3^{a}	0.7±0.2^{b}	0.5±0.1^{a}
670	1.5±0.7^{a}	5.6±1.5^{a}	1.5±0.4^{a}	1.6±0.4^{b}	1.1±0.3^{a}	0.5±0.2^{a}	0.5±0.1^{a}
1000	2.1±0.7^{b}	7.6±1.8^{b}	1.5±0.4^{a}	1.8±0.5^{c}	1.2±0.3^{a}	0.8±0.2^{c}	0.5±0.1^{a}
Maerua subcordata (mg/kg body weight)							
Control	2.4±0.0^{a}	5.3±0.7^{a}	1.7±0.07^{a}	1.0±0.05^{a}	0.9±0.0^{b}	0.8±0.0^{a}	0.4±0.0^{a}
450	2.5±0.7^{a}	5.6±1.5^{a}	1.8±0.5^{a}	1.1±0.3^{a}	0.8±0.3^{a}	0.8±0.2^{a}	0.4±0.1^{a}
670	2.6±0.0^{a}	5.8±0.2^{a}	1.8±0.0^{a}	1.1±0.1^{a}	0.9±0.1^{b}	0.8±0.0^{a}	0.5±0.0^{a}
1000	2.6±0.7^{a}	5.8±1.6^{a}	1.8±0.5^{a}	0.9±0.3^{a}	0.9±0.2^{b}	0.8±0.2^{a}	0.4±0.1^{a}
Pappea capensis (mg/kg body weight)							
Control	2.5±0.0^{a}	5.5±0.4^{a}	1.7±0.4^{a}	1.1±0.3^{a}	0.9±0.03^{a}	0.8±0.2^{a}	0.4±0.0^{a}
450	2.5±.0.7^{a}	5.7±1.6^{a}	1.8±0.5^{ab}	1.1±0.3^{a}	0.9±0.3^{a}	0.8±0.2^{a}	0.4±0.1^{a}
670	2.6±.0.7^{a}	5.7±1.5^{a}	1.8±0.5^{ab}	1.0±0.3^{a}	0.9±0.3^{a}	0.8±0.2^{a}	0.4±0.1^{a}
1000	2.7±.0.7^{b}	5.6±1.7^{a}	1.9±0.5^{b}	1.1±0.3^{a}	1.1±0.3^{b}	0.9±0.2^{b}	0.5±0.1^{a}

Results expressed as Mean ± Standard Deviation (SD) for five animals in each treatment; Values across treatments followed by the same superscript are not significantly different at $\rho \leq 0.05$.

Table 4.27 shows the effects of a daily intraperitoneal administration of aqueous plant extracts to mice for 28 days at 450, 670 and 1000 mg/kg body weight on the relative percent organ to total body weight. Results indicate that a daily intraperitoneal administration of aqueous extracts of *C. dependens* to mice for 28 days at 450, 670, and 1000 mg/kg body weight decreased the relative percent brain to body weight compared to that of the normal control mice group ($\rho < 0.05$). Extract-treated mice groups at 450 and 1000 mg/kg body weight caused a statistically similar relative percent brain to body weight. Extract-treated mice at 670 mg/kg body weight dose caused the highest decrease in relative percent brain to body weight compared to that of the normal control mice group (Table 4.27).

A daily intraperit**o**neal administration of aqueous extracts of *C. dependens* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight significantly increased the relative percent liver to body weight in the extract-treated mice groups compared to that of the normal control mice group. The extract-treated mice groups at 450, 670 and 1000 mg/kg body weight caused statistically similar effects to the relative percent liver to body weight (Table 4.27).

Intraperitoneal administration of aqueous extracts of *C. dependens* to mice daily for 28 days at 450, 670, and 1000 mg/kg body weight increased the relative percent lungs to body weight in the extract-treated mice groups at 450, and 670 mg/kg body weight doses relative to that of the normal control mice group. Further, the extract-treated mice groups at 450 and 670 mg/kg body weight doses caused a statistically similar relative

percent lung to body weight. In addition, the extract-treated mice groups at 670 and 1000 mg/kg body weight caused a statistically similar relative percent lung to body weight. Extract-treated mice group at 1000 mg/kg body weight dose caused a relative percent lung to body weight which was statistically similar to that of the normal control mice group ($\rho > 0.05$). Extract-treated mice groups at 450 mg/kg body weight caused the highest relative percent lungs to body weight compared to the normal control mice group ($\rho < 0.05$) (Table 4.27).

Intraperitoneal administration of aqueous extracts of *C. dependens* to mice daily for 28 days at 450, 670, and 1000 mg/kg body weight increased the relative percent testes to body weight in the extract-treated mice groups at 450, and 670 mg/kg body weight doses compared to that of the normal control mice group. Extract-treated mice groups at 450 and 670 mg/kg body weight caused a similar relative percent testes to body weight. However, the extract-treated mice groups at 670 and 1000 mg/kg body weight doses caused a statistically similar relative percent testes to body weight to that of the normal control mice group. Extract-treated mice group at 450 mg/kg body weight dose caused the highest relative percent testes to body weight compared to that of the normal control mice group (Table 4.27).

Intraperitoneal administration of aqueous extracts of *C. dependens* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight caused a statistically non-significant effect to the relative percent kidney, spleen, and heart to body weight in the extract-

treated mice groups at all the three tested doses compared to that of the control mice group (Table 4.27).

Intraperitoneal administration of aqueous extracts of *M. undata* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight significantly decreased the relative percent brain to body weight in the extract-treated mice groups compared to that of the normal control mice group. Extract-treated mice groups at 450, 670 and 1000 mg/kg body weight doses caused a statistically similar effect to the relative percent brain to body weight (Table 4.27).

Further, intraperitoneal administration of aqueous extracts of *M. undata* to mice daily for 28 days at 450, 670, and 1000 mg/kg body weight significantly increased the relative percent lungs to body weight in the extract-treated mice groups at 1000 mg/kg body weight compared to that of the normal control mice group. Extract-treated mice groups at 450 and 1000 mg/kg body weight caused a statistically similar effect to the relative percent lungs to body weight. Further, the extract-treated mice groups at 450 and 670 mg/kg body weight caused a statistically similar effect on the relative percent lungs to body weight compared to that of the normal control mice group (Table 4.27).

In addition, intraperitoneal administration of aqueous extracts of *M. undata* to mice daily for 28 days at 450, 670, and 1000 mg/kg body weight caused a non-significant effect to the extract treated mice group at 450 mg/kg body weight relative to that of the normal control mice group. However, this treatment significantly increased the relative percent heart to body weight to statistically similar levels in extract-treated mice groups

at 670 and 1000 mg/kg body weight doses compared to that of the normal control mice group (Table 4.27).

Intraperitoneal administration of aqueous extracts of *M. undata* to mice daily for 28 days at 450, 670, and 1000 mg/kg body weight caused a statistically non-significant effect to the relative percent liver, kidney, spleen, testes to body weight in the extract-treated mice groups at all the three tested doses compared to that of the normal control mice group (Table 4.27).

Intraperitoneal administration of aqueous extracts of *S. cordutum* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight significantly decreased the relative percent brain to body weight in the extract-treated mice groups compared to that of the normal control mice group. Extract-treated mice groups at 450 mg/kg body weight dose caused a significantly greater decrease in the relative percent brain to body weight than those at 670 and 1000 mg/kg body weight doses which caused a similar relative percent brain to body weight. Extract treated mice group at 450 mg/kg body weight dose caused the greatest decrease in the relative percent brain to body weight relative to that of the normal control mice group (Table 4.27).

Further, intraperitoneal administration of aqueous extracts of *S. cordutum* to mice daily for 28 days at 450, 670, and 1000 mg/kg body weight significantly increased the relative percent liver to body weight in the extract-treated mice groups at 670 and 1000 mg/kg body weight compared to that of the normal control mice group; this was similar

to the extract-treated mice group at 450 mg/kg body weight. Extract-treated mice groups at 670 mg/kg body weight caused a statistically significant decrease in the relative percent liver to body weight compared to the extract-treated mice group at 1000 mg/kg body weight. Extract-treated mice group at 1000 mg/kg body weight caused the greatest increase in the relative percent liver to body weight compared to that of the normal control mice group (Table 4.27).

In addition, intraperitoneal administration of aqueous extracts of *S. cordutum* to mice daily for 28 days at 450, 670, and 1000 mg/kg body weight caused a non-significant effect on the relative percent kidney to body weight in the extract-treated mice group at 670 mg/kg body weight compared to the normal control mice group. However, this extract-treatment at 450 mg/kg body weight significantly decreased the relative percent kidney to body weight compared to the normal control mice group. Extract-treated mice group at 1000 mg/kg body weight caused the highest increase in the relative percent kidney weight compared to that of the normal control mice group (Table 4.27).

Intraperitoneal administration of aqueous extracts of *S. cordutum* to mice daily for 28 days at 450, 670, and 1000 mg/kg body weight caused a non-significant effect on the relative percent lungs to body weight in the extract-treated mice group at 450 and 670 mg/kg body weight compared to the normal control mice group. However, this extract-treatment at 1000 mg/kg body weight significantly increased in the relative percent lung to body weight compared to the normal control mice group (Table 4.27).

Intraperitoneal administration of aqueous extracts of *S. cordutum* to mice daily for 28 days at 450, 670, and 1000 mg/kg body weight caused a non-significant effect on the relative percent spleen to body weight in the extract-treated mice group at 450 mg/kg body weight compared to the normal control mice group. However, this extract-treatment at 670 and 1000 mg/kg body weight caused a similar relative percent spleen to body weight but a significant increase in the relative percent spleen to body weight compared to the normal control mice group (Table 4.27).

Intraperitoneal administration of aqueous extracts of *S. cordutum* to mice daily for 28 days at 450, 670, and 1000 mg/kg body weight caused a non-significant effect on the relative percent heart to body weight in the extract-treated mice group at 450 and 670 mg/kg body weight compared to the normal control mice group. However, this extract-treated mice group at 1000 mg/kg body weight caused a significant increase in the relative percent heart to body weight compared to the normal control mice group (Table 4.27).

Intraperitoneal administration of aqueous extracts of *S. cordutum* to mice daily for 28 days at 450, 670, and 1000 mg/kg body weight caused a statistically non-significant effect to the relative percent testes to body weight in the extract-treated mice groups at all the three tested doses compared to that of the normal control mice group (Table 4.27).

Intraperitoneal administration of aqueous extracts of *M. subcordata* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight significantly increased the relative percent brain to body weight in the extract-treated mice groups compared to that of the normal control mice group. Extract-treated mice groups at 450 and 670 mg/kg body weight dose caused a non-significant effect on the relative percent brain to body weight but significantly lower relative percent to body weight compared to the extract-treated mice at 1000 mg/kg body weight. Extract treated mice group at 1000 mg/kg body weight dose caused the greatest increase in the relative percent brain to body weight relative to that of the normal control mice group (Table 4.27).

Further, intraperitoneal administration of aqueous extracts of *M. subcordata* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight significantly increased the relative percent liver to body weight in the extract-treated mice groups at 670 and 1000 mg/kg body weight compared to that of the control mice group; the effects of these two extracts treatment in mice was similar to that of the extract-treated mice group at 450 mg/kg body weight. Extract-treated mice groups at 450 mg/kg body weight caused a statistically non-significant effect in the relative percent liver to body weight compared to that of the normal control mice group. Extract-treated mice group at 1000 mg/kg body weight caused the greatest increase in the relative percent liver to body weight compared to that of the normal control mice group (Table 4.27).

In addition, intraperitoneal administration of aqueous extracts of *M. subcordata* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight caused a non-significant

effect on the relative percent kidney to body weight in the extract-treated mice group at 450, and 670 mg/kg body weight compared to the normal control mice group. However, this extract-treatment at 1000 mg/kg body weight significantly increased the relative percent kidney to body weight compared to the normal control mice group. Extract-treated mice group at 670 mg/kg body weight caused a significantly lower increase in the relative percent kidney to body weight compared to the extract-treated mice group at 1000 mg/kg body weight. The extract-treated mice group at 1000 mg/kg body weight caused the highest increase in the relative percent kidney weight compared to that of the normal control mice group (Table 4.27).

Intraperitoneal administration of aqueous extracts of *M. subcordata* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight caused a non-significant effect on the relative percent spleen to body weight in the extract-treated mice group at 450 mg/kg body weight compared to that of the normal control mice group. However, the extract-treated mice group at 670 mg/kg body weight caused a similar effect to the relative percent spleen to body weight to that of extract-treated mice group at 1000 mg/kg body weight. Extract-treated mice group at 1000 mg/kg body weight caused the highest relative percent spleen to body weight relative to normal control mice group (Table 4.27).

Intraperitoneal administration of aqueous extracts of *M. subcordata* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight caused a non-significant effect on the relative percent heart to body weight in the extract-treated mice group at 450 and 670

mg/kg body weight compared to the normal control mice group. However, the extract-treated mice group at 1000 mg/kg body weight caused the highest relative percent heart to body weight compared to the normal control mice group (Table 4.27).

Intraperitoneal administration of aqueous extracts of *M. subcordata* at 450, 670 and 1000 mg/kg body weight to mice daily for 28 days caused a statistically non-significant effect to the relative percent lungs and testes to body weight in the extract-treated mice groups at all the three tested doses compared to that of the normal control mice group (Table 4.27).

Intraperitoneal administration of aqueous extracts of *P. capensis* to mice at 450, 670 and 1000 mg/kg body weight daily for 28 days significantly increased the relative percent brain, and lung to body weight in the extract-treated mice groups at 1000 mg/kg body weight compared to that of the normal control mice group. However, the extract-treated mice groups at 450 and 670 mg/kg body weight dose caused a non-significant effect on the relative percent brain, and lung to body weight compared to that of the normal control mice group. Extract treated mice group at 1000 mg/kg body weight dose caused the greatest increase in the relative percent brain, and lung to body weight relative to that of the normal control mice group (Table 4.27).

Further, intraperitoneal administration of aqueous extracts of *P. capensis* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight significantly increased the relative percent liver to body weight in the extract-treated mice groups at 670 and 1000 mg/kg

body weight compared to that of the control mice group; the effect of extract-treatment to mice at 450 mg/kg body weight was similar to that of the normal control mice group. Extract-treated mice group at 450 and 670 mg/kg body weight caused a similar increase in the relative percent liver to body weight. Further, extract-treated mice group at 670 and 1000 mg/kg body weight caused a similar increase in the relative percent liver to body weight. The extract-treated mice group at 1000 mg/kg body weight caused the greatest increase in the relative percent liver to body weight compared to that of the normal control mice group (Table 4.27).

In addition, intraperitoneal administration of aqueous extracts of *P. capensis* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight caused a significant relative percent kidney to body weight in the extract-treated mice at all the three tested extract doses. Extract-treated mice groups at 450 and 670 mg/kg body weight caused a similar increase in the relative percent kidney to body weight. Extract-treated mice group at 1000 mg/kg body weight caused the greatest increase in the relative percent kidney to body weight compared to that of the normal control mice group (Table 4.27).

Intraperitoneal administration of aqueous extracts of *P. capensis* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight caused a non-significant effect on the relative percent spleen , testes and heart to body weight in the extract-treated mice group at 450, and 670 mg/kg body weight compared to that of the normal control mice group. However, the extract-treated mice group at 1000 mg/kg body weight caused the

greatest increase in the relative percent spleen, testes, and heart to body weight relative to normal control mice group (Table 4.27).

Table 4.27: Effects of intraperitoneal administration of aqueous plants extracts to mice daily for 28 days on the percent organ to body weight

Treatment	Percent organ to body weight						
	Brain	Liver	Kidney	Lungs	Spleen	Testes	Heart
Chasmanthera dependens (mg/kg body weight)							
Control	2.5±0.1^{c}	5.3±0.2^{a}	1.7±0.1^{a}	1.0±0.0^{a}	0.9±0.0^{a}	0.8±0.0^{a}	0.4±0.0^{a}
450	1.7±0.7^{ab}	7.9±2.3^{b}	1.8±0.5^{a}	2.6±0.9^{c}	1.0±0.3^{a}	1.1±0.3^{b}	0.6±0.2^{a}
670	1.3±0.7^{a}	7.0±2.2^{b}	1.5±0.5^{a}	2.1±0.9^{bc}	0.7±0.3^{a}	0.9±0.3^{ab}	0.4±0.2^{a}
1000	1.7±0.7^{ab}	6.9±2.4^{b}	1.6±0.5^{a}	1.5±0.8^{ab}	0.8±0.3^{a}	0.7±0.3^{a}	0.5±0.2^{a}
Mayrtenus undata (mg/kg body weight)							
Control	2.5±0.1^{c}	5.3±0.2^{a}	1.7±0.1^{a}	1.0±0.0^{a}	0.9±0.0^{a}	0.8±0.0^{a}	0.4±0.0^{a}
450	1.1±0.8^{a}	4.8±1.5^{a}	1.4±0.5^{a}	1.6±0.4^{ab}	0.6±0.3^{a}	0.5±0.2^{a}	0.3±0.1^{a}
670	1.2±0.7^{a}	5.3±1.5^{a}	1.3±0.4^{a}	1.2±0.4^{ab}	0.7±0.3^{a}	0.6±0.2^{a}	0.5±0.1^{b}
1000	1.2±0.7^{a}	5.4±1.5^{a}	1.4±0.4^{a}	1.7±0.4^{b}	0.7±0.3^{a}	0.5±0.2^{a}	0.5±0.1^{b}
Syzigium cordatum (mg/kg body weight)							
Control	2.5±0.1^{c}	5.3±0.2^{a}	1.7±0.1^{b}	1.0±0.0^{a}	0.9±0.0^{a}	0.8±0.0^{a}	0.4±0.0^{a}
450	1.5±0.7^{a}	5.7±1.6^{a}	1.4±0.5^{a}	1.5±0.4^{b}	1.0±0.3^{ab}	0.7±0.2^{a}	0.5±0.1^{ab}
670	1.9±0.6^{b}	7.3±1.8^{b}	1.6±0.4^{b}	1.6±0.5^{b}	1.1±0.3^{c}	0.7±0.2^{a}	0.5±0.1^{bc}
1000	2.1±0.6^{b}	9.3±2.4^{c}	2.0±0.5^{c}	1.9±0.5^{c}	1.1±0.3^{c}	0.8±0.2^{a}	0.6±0.2^{c}
Maerua subcordata (mg/kg body weight)							
Control	2.4±0.7^{a}	5.3±1.6^{a}	1.7±0.5^{a}	1.0±0.3^{a}	0.9±0.3^{a}	0.8±0.2^{a}	0.4±0.1^{a}
450	2.5±0.7^{ab}	5.6±1.5^{ab}	1.7±0.5^{a}	1.1±0.3^{a}	0.8±0.3^{ab}	0.8±0.2^{a}	0.4±0.1^{a}
670	2.6±0.0^{ab}	5.7±0.2^{b}	1.8±0.0^{ab}	1.1±0.1^{a}	0.8±0.1^{c}	0.8±0.0^{a}	0.4±0.0^{ab}
1000	2.6±0.7^{c}	5.9±1.6^{b}	1.9±0.5^{c}	1.1±0.3^{a}	1.0±0.2^{bc}	0.8±0.2^{a}	0.5±0.1^{b}
Pappea capensis (mg/kg body weight)							
Control	2.4±0.7^{a}	5.3±1.6^{a}	1.7±0.5^{a}	1.0±0.3^{a}	0.9±0.3^{a}	0.8±0.2^{a}	0.4±0.1^{a}
450	2.6±0.7^{ab}	5.7±1.6^{ab}	1.8±0.5^{b}	1.1±0.3^{ab}	0.8±0.3^{a}	0.8±0.2^{a}	0.4±0.1^{a}
670	2.6±0.7^{ab}	5.8±1.6^{bc}	1.8±0.5^{b}	1.1±0.3^{c}	0.9±0.3^{a}	0.8±0.2^{a}	0.4±0.1^{a}
1000	2.7±0.7^{b}	6.3±1.6^{c}	2.0±0.5^{c}	1.2±0.3^{c}	1.1±0.3^{b}	0.9±0.2^{b}	0.5±0.1^{c}

Results expressed as Mean ± Standard Deviation (SD) for five animals in each treatment; Values across treatments followed by the same superscript are not significantly different at $\rho \leq 0.05$.

4.5 Effects of a daily orally and intraperitoneally administered aqueous plant extracts to mice for 28 days at high doses on red blood cells, hemoglobin, platelets and their related indices in mice

The hematological parameters that were measured for assessment of toxicity in the erythrocyte series included RBC ($x10^{12}$/L), HB (g/dL), PCV (%), MCH (pg), MCHC (g/dL), and MCV (fL). Platelets ($x10^{9}$/L) were also measured to assess the thrombocyte series. Table 4.28 and 4.29 shows the results of the effects of a daily oral and intraperitoneal administration of aqueous extracts at the three high non-therapeutic doses for *C. dependens*. Results of a daily oral administration of the aqueous extracts of *C. dependens* to mice for 28 days at 450, 670, and 1000 mg/kg body weight caused a significant increase in RBC and Hb levels at 670 and 1000 mg/kg body weight dose relative to the extract-treated mice group at 450 mg/kg body weight dose. Extract-treated mice groups at 670 and 1000 mg/kg body weight doses caused a similar effect to the levels of RBC and Hb to those of normal control mice groups. Extract-treated mice group at 450 mg/kg body weight cause similar effects to the levels of RBC and Hb to those of the normal control mice group. Further, a daily oral administration of aqueous extracts of C. dependens to mice for 28 days at 450, 670, and 1000 mg/kg body weight caused a significant increase in the levels of PCV at 670 and 1000 mg/kg body weight doses relative to that of the normal control mice group. In addition, the extract-treated mice group at 450 mg/kg body weight caused a significant decrease in the level of PCV relative to the normal control mice group. Extract-treated mice groups at 670 and 1000 mg/kg body weight doses caused a similar effect to the level of PCV which was significantly greater than that of the extract-treated mice group at 450 mg/kg body weight dose. Oral administration of aqueous extracts of *C. dependens* to mice for 28

days at 450, 670, and 1000 mg/kg body weight caused a significant increase in the levels of MCV in extract-treated mice groups at 450 and 1000 mg/kg body weight doses relative to that of the normal control mice group. Extract-treated mice groups at 450 and 670 mg/kg body weight caused a similar effect to level of MCV which was significantly different from that of the extract-treated mice group at 1000 mg/kg body weight. Extract-treated mice group at 670 mg/kg body weight caused a similar effect to the level of MCV caused by the normal control mice group. Extract-treated mice groups at 450 and 670 mg/kg body weight caused similar effects to the levels of MCH to those caused by the normal control mice group which were significantly lower relative to the extract-treated mice group at 1000 mg/kg body weight. Extract-treated mice group 670 and 1000 mg/kg body weight caused similar effects to the levels of MCHC to those caused by the normal control mice group. Extract-treated mice group at 450 mg/kg body weight caused a significant reduction to the levels of MCHC relative to that caused by the extract-treated mice group at 1000 mg/kg body weight and the normal control mice group. Extract-treated mice group at 670 and 1000 mg/kg body weight caused a similar effect to the level of PLT to that caused by the normal control mice group. Extract-treated mice group at 450 mg/kg body weight caused a reduction to the level of PLT relative to that caused by the normal control mice group. Extract-treated mice group at 450 and 1000 mg/kg body caused a similar effect to the levels of PLT (Table 4.28).

Table 4.28: Effects of a daily oral administration of aqueous extracts of *Chasmanthera dependens* in mice for four weeks at high doses on erythrocytes, hemoglobin, platelets and their related indices

Treatment	Hematological parameters						
	Hb (g/dL)	**RBC (x10^{12}/L)**	**PCV (%)**	**MCV (fL)**	**MCH (pg)**	**MCHC (g/dL)**	**PLT (x10^{9}/L)**
***Chasmanthera dependens* (mg/kg body weight)**							
Control	10.8 ± 2.4^{AB}	7.7 ± 1.6^{AB}	33.3 ± 7.3^{A}	43.4 ± 1.0^{A}	14.6 ± 0.3^{A}	32.4 ± 0.5^{B}	323.0 ± 61.0^{B}
450	8.0 ± 2.0^{A}	5.5 ± 1.3^{A}	25.7 ± 6.3^{CD}	47.0 ± 1.1^{BC}	14.5 ± 0.3^{A}	30.9 ± 0.5^{A}	214.8 ± 21.1^{A}
670	12.2 ± 1.6^{B}	8.5 ± 1.0^{B}	38.6 ± 4.7^{B}	45.3 ± 2.2^{AB}	14.3 ± 0.5^{A}	31.6 ± 0.9^{AB}	323.0 ± 61.0^{B}
1000	12.8 ± 1.2^{B}	8.3 ± 0.7^{B}	40.0 ± 3.5^{B}	48.3 ± 0.5^{C}	15.4 ± 0.2^{B}	32.0 ± 0.3^{B}	344.6 ± 52.0^{AB}

Values expressed as Mean ± SD. Means within respective treatments followed by similar upper case letters are not significantly different at $\rho \leq 0.05$. Hb-Hemoglobin, RBC-Red blood cells, PCV-Packed cell volume, MCV-Mean cell volume, MCH- mean cell hemoglobin, MCHC-Mean cell hemoglobin concentration and PLT-Platelets.

Intraperitoneal administration of aqueous extracts of *C. dependens* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight caused a significant reduction to the levels of RBC and Hb at 450 mg/kg body weight relative to the normal control mice group. Extract-treated mice groups at 670 and 1000 mg/kg body weight significantly reduced the levels of RBC and Hb to levels similar to those of the normal control mice group. Extract-treated mice group at all the three extract doses and the normal control mice group caused similar effects to the levels of PCV and MCHC. Extract-treated mice at 450, and 670 mg/kg body weight caused similar effects to the levels of MCV to those caused by the normal control mice group. Extract-treated mice groups at 450 and 670 mg/kg body weight caused similar effects to the levels of MCV which were significantly lower to those of the extract-treated mice at 1000 mg/kg body weight. Extract-treated mice group at 1000 mg/kg body weight caused similar effects of MCV to those of normal control mice group. Extract-treated mice group at 670, and 1000 mg/kg body weight caused similar effects to the levels of MCH to those caused by the normal control mice group. Extract-treated mice group at 450 mg/kg body weight caused a significantly lower levels of MCH relative to the extract-treated mice at 1000 mg/kg body weight (Table 4.29).

Table 4.29: Effects of a daily intraperitoneal administration of aqueous extracts of *Chasmanthera dependens* in mice for four weeks at high doses on erythrocytes, hemoglobin, platelets and their related indices

Treatment	Hematological parameters						
	Hb (g/dL)	**RBC (x10^{12}/L)**	**PCV (%)**	**MCV (fL)**	**MCH (pg)**	**MCHC (g/dL)**	**PLT (x10^{9}/L)**
***Chasmanthera dependens* (mg/kg body weight)**							
Control	12.1 ± 0.7^{B}	8.2 ± 0.4^{B}	37.0 ± 2.3^{A}	45.3 ± 2.0^{AB}	14.7 ± 0.5^{AB}	32.6 ± 0.6^{A}	338.8 ± 42.1^{A}
450	8.1 ± 1.7^{A}	5.7 ± 1.2^{A}	25.3 ± 5.5^{A}	44.5 ± 0.9^{A}	14.1 ± 0.7^{A}	31.9 ± 1.3^{A}	267.6 ± 92.4^{A}
670	11.6 ± 1.5^{B}	8.0 ± 0.7^{B}	36.4 ± 3.8^{A}	45.8 ± 1.5^{AB}	14.6 ± 0.7^{AB}	31.9 ± 0.9^{A}	380.0 ± 67.0^{A}
1000	13.4 ± 0.8^{B}	8.7 ± 0.5^{B}	41.6 ± 2.5^{A}	47.7 ± 1.1^{B}	15.3 ± 0.4^{B}	32.2 ± 0.5^{A}	366.2 ± 69.3^{A}

Values expressed as Mean ± SD. Means within respective treatments followed by similar upper case letters are not significantly different at $\rho \leq 0.05$. Hb-Hemoglobin, RBC-Red blood cells, PCV-Packed cell volume, MCV-Mean cell volume, MCH-Mean cell hemoglobin, MCHC-Mean cell hemoglobin concentration and PLT-Platelets.

Oral administration of aqueous extracts of *M. undata* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight caused similar effects to the levels of RBC, Hb, PCV, and MCHC which were significantly lower relative to that of the normal control mice group. Extract-treated mice group at 450, 670 and 1000 mg/kg body weight caused similar effects to the levels of MCV which was significantly higher relative to that of the normal control mice group (Table 4.30). Extract-treated mice group at 450, 670 and 1000 mg/kg body weight caused non-significant effect to the levels of MCH and PLT relative to that of the normal control mice group (Table 4.30).

Table 4.30: Effects of a daily oral administration of aqueous extracts of *M. undata* in mice for four weeks at high doses on erythrocytes, hemoglobin, platelets and their related indices

Treatment	Hematological parameters						
	Hb (g/dL)	**RBC (x10^{12}/L)**	**PCV (%)**	**MCV (fL)**	**MCH (pg)**	**MCHC (g/dL)**	**PLT (x10^{9}/L)**
***Mayrtenus undata* (mg/kg body weight)**							
Control	10.8 ± 2.4^{B}	7.7 ± 1.6^{B}	33.3 ± 7.26^{B}	43.4 ± 1.0^{B}	14.6 ± 0.3^{A}	32.4 ± 0.5^{B}	323.0 ± 61.0^{A}
450	5.0 ± 0.9^{A}	3.7 ± 0.7^{A}	18.6 ± 2.9^{A}	50.8 ± 1.9^{A}	13.5 ± 0.3^{A}	26.8 ± 1.0^{A}	321.0 ± 25.2^{A}
670	4.8 ± 1.8^{A}	3.5 ± 1.2^{A}	17.6 ± 5.8^{A}	50.9 ± 1.2^{A}	13.6 ± 1.0^{A}	26.6 ± 2.2^{A}	357.8 ± 103.3^{A}
1000	5.8 ± 0.8^{A}	4.5 ± 0.5^{A}	21.5 ± 1.7^{A}	48.1 ± 2.5^{A}	12.9 ± 1.0^{A}	26.9 ± 1.9^{A}	320.6 ± 28.9^{A}

Values expressed as Mean ± SD. Means within respective treatments followed by similar upper case letters are not significantly different at $\rho \leq 0.05$. Hb-Hemoglobin, RBC-Red Blood Cells, PCV-Packed Cell Volume, MCV-Mean Cell Volume, MCH-Mean Cell Hemoglobin, MCHC-Mean Cell Hemoglobin Concentration and PLT-Platelets.

Intraperitoneal administration of aqueous extracts of *M. undata* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight caused similar effects to the levels of RBC, Hb, PCV, and MCHC which were significantly lower relative to that of the normal control mice group. Extract-treated mice group at 450, 670 and 1000 mg/kg body weight caused non-significant effect to the levels of MCV, MCH and PLT relative to that of the normal control mice group (Table 4.31).

Table 4.31: Effects of a daily intraperitoneal administration of aqueous extracts of *Mayrtenus undata* in mice for four weeks at high doses on erythrocytes, hemoglobin, platelets and their related indices

Treatment	Hematological parameters						
	Hb (g/dL)	**RBC (x10^{12}/L)**	**PCV (%)**	**MCV (fL)**	**MCH (pg)**	**MCHC (g/dL)**	**PLT (x10^{9}/L)**
***Mayrtenus undata* (mg/kg body weight)**							
Control	12.1 ± 0.7^{B}	8.2 ± 0.4^{B}	37.0 ± 2.3^{B}	45.3 ± 2.0^{A}	14.7 ± 0.5^{A}	32.6 ± 0.6^{B}	338.8 ± 42.1^{A}
450	4.6 ± 2.2^{A}	3.4 ± 1.5^{A}	17.3 ± 7.3^{A}	52.5 ± 3.3^{A}	13.5 ± 0.6^{A}	25.9 ± 2.5^{A}	303.0 ± 78.1^{A}
670	5.8 ± 1.2^{A}	4.2 ± 1.2^{A}	19.8 ± 4.4^{A}	47.9 ± 3.5^{A}	13.1 ± 0.3^{A}	26.1 ± 2.7^{A}	357.8 ± 103.3^{A}
1000	5.0 ± 1.7^{A}	4.9 ± 1.8^{A}	21.8 ± 5.0^{A}	49.7 ± 5.2^{A}	13.4 ± 0.7^{A}	27.1 ± 1.7^{A}	312.6 ± 66.3^{A}

Values expressed as Means ± SD. Means within respective treatments followed by similar upper case letters are not significantly different at $\rho \leq 0.05$. Hb-Hemoglobin, RBC-Red Blood Cells, PCV-Packed Cell Volume, MCV-Mean Cell Volume, MCH-Mean Cell Hemoglobin, MCHC-Mean Cell Hemoglobin Concentration and PLT-Platelets.

Oral administration of aqueous extracts of *S. cordutum* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight caused a non-significant effect in the levels of Hb, PCV, MCH and MCHC relative to that of the normal control mice group ($\rho > 0.05$). Extract-treated mice group at 450, 670 and 1000 mg/kg body weight caused a non-significant effect on the levels of RBC and PLT ($\rho > 0.05$) which is significantly higher than that of the normal control mice group ($\rho < 0.05$). Extract-treated mice group at 670 mg/kg body weight caused a non-significant effect in the level of RBC ($\rho > 0.05$) relative to that of the normal control mice group ($\rho > 0.05$). Extract-treated mice group at 450 mg/kg body weight caused a non-significant effect to the levels of PLT ($\rho > 0.05$) relative to that of the normal control mice group ($\rho > 0.05$). Extract-treated mice group at 450, 670 and 1000 mg/kg body weight cause a non-significant effect on the levels of MCV ($\rho > 0.05$) which were significantly higher than that of the normal control mice group ($\rho < 0.05$) (Table 4.32).

Table 4.32: Effects of a daily oral administration of aqueous extracts of *S. cordutum* in mice for four weeks at high doses on erythrocytes, hemoglobin, platelets and their related indices

Treatment	Hematological parameters						
	Hb (g/dL)	**RBC (x10^{12}/L)**	**PCV (%)**	**MCV (fL)**	**MCH (pg)**	**MCHC (g/dL)**	**PLT (x10^{9}/L)**
***Syzigium cordutu*m (mg/kg body weight)**							
Control	10.8±2.4^{A}	7.7±1.6^{B}	33.3±7.3^{A}	43.4±1.0^{B}	14.6±0.3^{A}	32.4±0.5^{A}	323.0±61.0^{B}
450	11.6±2.6^{A}	7.8±1.8^{A}	37.5±9.1^{A}	48.2±1.0^{A}	15.0±0.5^{A}	31.0±0.9^{B}	761.2±198.8^{AB}
670	11.9±0.7^{A}	7.9±0.5^{AB}	36.4±2.5^{A}	46.2±1.6^{A}	15.0±0.6^{A}	32.4±1.2^{B}	580.2±207.6^{A}
1000	12.4±1.5^{A}	8.1±0.9^{A}	40.3±5.5^{A}	49.7±3.7^{A}	15.3±0.9^{A}	30.6±1.0^{B}	568.8±131.7^{A}

Values expressed as Mean ± SD. Means within respective treatments followed by similar upper case letters are not significantly different at $\rho \leq 0.05$. Hb- Hemoglobin, RBC- Red blood cells, PCV- Packed cell volume, MCV- Mean cell volume, MCH- mean cell hemoglobin, MCHC- Mean cell hemoglobin concentration and PLT- Platelets.

Intraperitoneal administration of aqueous extracts of *S. cordutum* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight caused a non-significant effect on the levels of Hb, PCV and MCV relative to that of the normal control mice group. Extract-treated mice group at 450 mg/kg body weight caused a significant reduction in the levels of RBC relative that of the normal control mice group. Extract-treated mice group at a dose of 450, 670 and 1000 mg/kg body weight caused a non-significant effect on the levels of RBC. Extract-treated mice group at 670 and 1000 mg/kg body weight caused a non-significant effect to the levels of RBC which were similar to those of the normal control mice group. Extract-treated mice group at 450 mg/kg body weight caused a significant increase to the levels of MCH relative to those of the normal control mice group. Extract-treated mice group at 1000 mg/kg body weight caused a significant reduction in the levels of MCH relative to that of the normal control mice group. Extract-treated mice group at 450 and 670 mg/kg body weight caused a similar effect to the levels of MCH. Extract-treated mice group at 670 and 1000 mg/kg body weight caused a similar effect to the levels of MCH. Extract-treated mice groups at 450, 670 and 1000 mg/kg body weight caused similar effects to the levels of MCHC which were significantly lower relative to those of the normal control mice group.

Extract-treated mice group at 450 and 1000 mg/kg body weight caused similar effects to the levels of PLT which were significantly higher than those of the normal control mice group. Extract-treated mice groups at 450, 670 and 1000 mg/kg body weight caused similar effects to the levels of PLT. Extract-treated mice group at 670 mg/kg body

weight caused a non-significant effect on the levels of PLT relative to that of the normal control mice group (Table 4.33).

Table 4.33: Effects of a daily intraperitoneal administration of aqueous extracts of *S. cordutum* in mice for four weeks at high doses on erythrocytes, hemoglobin, platelets and their related indices

Treatment	Hematological parameters						
	Hb (g/dL)	**RBC (x10^{12}/L)**	**PCV (%)**	**MCV (fL)**	**MCH (pg)**	**MCHC (g/dL)**	**PLT (x10^{3}/L)**
***Syzigium cordutum* (mg/kg body weight)**							
Control	12.1±0.7^{A}	8.2±0.4^{B}	37.0±2.3^{A}	45.3±2.0^{A}	14.7±0.5^{C}	32.6±0.6^{A}	338.8±42.1^{B}
450	10.8±0.7^{A}	6.9±0.5^{A}	34.4±1.0^{A}	50.2±2.4^{A}	15.8±0.5^{BC}	31.5±1.7^{B}	524.3±287.7^{A}
670	10.9±1.9^{A}	7.9±1.4^{AB}	35.0±6.4^{A}	44.4±2.2^{A}	13.8±0.4^{AB}	31.1±0.9^{B}	526.4±194.3^{AB}
1000	12.3±1.6^{A}	8.6±1.3^{AB}	39.1±4.8^{A}	45.9±2.8^{A}	13.6±1.0^{A}	31.5±1.1^{B}	568.8±131.7^{A}

Values expressed as Mean ± SD. Means within respective treatments followed by similar upper case letters are not significantly different at $\rho \leq 0.05$. Hb-Hemoglobin, RBC-Red blood cells, PCV-Packed cell volume, MCV-Mean cell volume, MCH-Mean cell hemoglobin, MCHC-Mean cell hemoglobin concentration and PLT-Platelets.

Oral administration of aqueous extracts of *M. subcordata* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight caused a non-significant effect on the levels of Hb and MCH relative to those of the normal control mice group. Extract-treated mice groups at 450, 670 and 1000 mg/kg body weight caused similar effects to the levels of RBC, PCV, and MCV which were significantly lower than those of the normal control mice group. Extract-treated mice group at 450, 670 and 1000 mg/kg body weight caused a similar effect to the levels of MCHC which was significantly higher than those of the normal control mice group ($\rho < 0.05$). Extract-treated mice group at 1000 mg/kg body weight caused a significant reduction in the levels of PLT relative to that of the normal control mice group ($\rho < 0.05$). Extract-treated mice group at 450, 670 and 1000 mg/kg body weight caused similar effects to the levels of PLT ($\rho > 0.05$). Extract-treated mice group at 450 and 670 mg/kg body weight caused similar effects to the levels of PLT which were comparable to those of the normal control mice group ($\rho > 0.05$) (Table 4.34).

Table 4.34: Effects of a daily oral administration of aqueous extracts of *M. subcordata* in mice for four weeks at high doses on erythrocytes, hemoglobin, platelets and their related indices

Treatment	Hematological parameters						
	Hb (g/dL)	**RBC (x10^{12}/L)**	**PCV (%)**	**MCV (fL)**	**MCH (pg)**	**MCHC (g/dL)**	**PLT (x10^{9}/L)**
***Maerua subcordata* (mg/kg body weight)**							
Control	12.2 ± 1.5^{A}	9.9 ± 0.7^{B}	51.5 ± 10.0^{B}	66.3 ± 6.8^{B}	16.4 ± 1.9^{A}	23.1 ± 2.7^{A}	1019.2 ± 106.2^{B}
450	10.4 ± 1.1^{A}	5.9 ± 0.8^{A}	30.4 ± 4.4^{A}	51.6 ± 1.5^{A}	17.6 ± 1.0^{A}	34.2 ± 2.6^{B}	745.0 ± 181.7^{AB}
670	11.8 ± 1.5^{A}	6.5 ± 0.8^{A}	32.9 ± 3.5^{A}	50.5 ± 1.0^{A}	18.1 ± 0.6^{A}	35.9 ± 1.7^{B}	746.2 ± 234.6^{AB}
1000	11.6 ± 0.6^{A}	6.5 ± 0.3^{A}	35.0 ± 3.0^{A}	53.8 ± 3.1^{A}	17.8 ± 0.7^{A}	33.3 ± 3.2^{B}	616.4 ± 108.2^{A}

Values expressed as Mean ± SD. Means within respective treatments followed by similar upper case letters are not significantly different at $\rho \leq 0.05$. Hb-Hemoglobin, RBC-Red blood cells, PCV-Packed cell volume, MCV-Mean cell volume, MCH-Mean cell hemoglobin, MCHC-Mean cell hemoglobin concentration and PLT-Platelets.

Intraperitoneal administration of aqueous extracts of *M. subcordata* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight caused similar effects to the level of Hb which was comparable to that of the normal control mice group ($\rho > 0.05$). Extract-treated mice group at 450, 670 and 1000 mg/kg body weight caused similar effects to the levels of RBC, PCV, MCV and PLT ($\rho > 0.05$) which were significantly lower than those of the normal control mice group ($\rho < 0.05$). Extract-treated mice at 450, 670 and 1000 mg/kg body weight caused similar effects to the levels of MCHC ($\rho > 0.05$) which were significantly higher than those of the normal control mice group ($\rho < 0.05$). Extract-treated mice group at 670 mg/kg body weight caused a significant increase in the levels of MCH compared to those of the normal control mice group ($\rho < 0.05$). Extract-treated mice groups at 450, 670 and 1000 mg/kg body weight caused similar effects in the levels of MCH ($\rho > 0.05$). Extract-treated mice groups at 450 and 1000 mg/kg body weight caused similar effects to the levels of MCH which were comparable to those of the control mice group ($\rho > 0.05$) (Table 4.35).

Table 4.35: Effects of a daily intraperitoneal administration of aqueous extracts of *M. subcordata* in mice for four weeks at high doses on erythrocytes, hemoglobin, platelets and their related indices

Treatment	Hematological parameters						
	Hb (g/dL)	**RBC (x10^{12}/L)**	**PCV (%)**	**MCV (fL)**	**MCH (pg)**	**MCHC (g/dL)**	**PLT (x10^{9}/L)**
***Maerua subcordata* (mg/kg body weight)**							
Control	12.0 ± 1.5^{A}	9.2 ± 1.0^{B}	52.8 ± 10.8^{B}	68.1 ± 8.0^{B}	16.4 ± 1.7^{A}	23.7 ± 2.1^{A}	1040.4 ± 109.4^{B}
450	10.1 ± 1.5^{A}	5.7 ± 0.8^{A}	29.1 ± 3.6^{A}	51.4 ± 2.1^{A}	17.9 ± 0.8^{AB}	34.8 ± 2.6^{B}	727.2 ± 110.2^{A}
670	11.5 ± 0.3^{A}	6.3 ± 0.3^{A}	32.5 ± 1.4^{A}	52.0 ± 0.7^{A}	18.5 ± 0.6^{B}	35.6 ± 1.1^{B}	595.8 ± 25.3^{A}
1000	11.6 ± 0.7^{A}	6.7 ± 0.3^{A}	35.6 ± 1.2^{A}	53.3 ± 1.9^{A}	17.3 ± 0.5^{AB}	32.5 ± 1.7^{B}	645.2 ± 131.9^{A}

Values expressed as Mean ± SD. Means within respective treatments followed by similar upper case letters are not significantly different at $\rho \leq 0.05$. Hb-Hemoglobin, RBC-Red blood cells, PCV-Packed cell volume, MCV-Mean cell volume, MCH-Mean cell hemoglobin, MCHC-Mean cell hemoglobin concentration and PLT-Platelets.

Oral administration of aqueous extracts of *P. capensis* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight caused similar effects to the levels of RBC, Hb, PCV, MCH, MCHC, and PLT which were comparable to those of normal control mice group. Extract-treated mice group at 450 mg/kg body weight significantly reduced the levels of MCH relative to that of the normal control mice group ($\rho < 0.05$). Extract-treated mice groups at 450, 670 and 1000 mg/kg body weight caused similar effects to the levels of MCH ($\rho > 0.05$). Extract-treated mice groups at 670 and 1000 mg/kg body weight caused similar effects to the levels of MCH which are comparable to those of the normal control mice group ($\rho > 0.05$) (Table 4.36).

Table 4.36: Effects of a daily oral administration of aqueous extracts of *P. capensis* in mice for four weeks at high doses on erythrocytes, hemoglobin, platelets and their related indices

Treatment	Hematological parameters						
	Hb (g/dL)	**RBC (x10^{12}/L)**	**PCV (%)**	**MCV (fL)**	**MCH (pg)**	**MCHC (g/dL)**	**PLT (x10^{9}/L)**
Pappea capensis(mg/kg body weight)							
Control	12.2±1.5^{A}	9.9±0.7^{A}	51.5±9.9^{A}	66.3±6.8^{B}	16.4±1.9^{A}	23.1±2.7^{A}	1019.2±106.2^{A}
450	11.7±1.2^{A}	17.3±8.4^{A}	47.3±2.3^{A}	52.6±6.0^{A}	14.9±2.9^{A}	25.8±1.2^{A}	950.4±81.5^{A}
670	12.6±2.9^{A}	9.1±1.0^{A}	49.8±18.5^{A}	61.8±9.1^{AB}	15.3±1.7^{A}	23.2±3.8^{A}	1021.6±117.4^{A}
1000	12.7±1.0^{A}	8.4±1.0^{A}	55.4±5.7^{A}	65.2±7.7^{AB}	14.9±1.2^{A}	22.4±1.9^{A}	1095.2±127.4^{A}

Values expressed as Mean ± SD. Means within respective treatments followed by similar upper case letters are not significantly different at $\rho \leq 0.05$. Hb- Heamoglobin, RBC- Red blood cells, PCV- Packed cell volume, MCV- Mean cell volume, MCH- mean cell heamoglobin, MCHC- Mean cell heamoglobin concentration and PLT- Platelets.

Intraperitoneal administration of aqueous extracts of *P. capensis* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight caused statistically similar effects to the levels of RBC, Hb, PCV, MCH, MCHC, MCV and PLT which were comparable to those of the normal control mice group ($p > 0.05$) (Table 4.37).

Table 4.37: Effects of a daily intraperitoneal administration of aqueous extracts of *P. capensis* in mice for four weeks at high doses on erythrocytes, hemoglobin, platelets and their related indices

Treatment	Hematological parameters						
	Hb (g/dL)	**RBC (x10^{12}/L)**	**PCV (%)**	**MCV (fL)**	**MCH (pg)**	**MCHC (g/dL)**	**PLT (x10^{9}/L)**
***Pappea capensis* (mg/kg body weight)**							
Control	12.0±1.5^{A}	9.2±1.0^{A}	52.8±10.8^{A}	68.1±8.0^{A}	16.4±1.6^{A}	23.7±2.1^{A}	1040.4±109.4^{A}
450	12.8±1.1^{A}	9.4±0.8^{A}	47.3±2.3^{A}	54.7±5.3^{A}	15.4±2.0^{A}	26.9±1.5^{A}	927.6±92.2^{A}
670	12.8±2.5^{A}	9.0±1.0^{A}	50.6±18.0^{A}	61.9±8.4^{A}	14.6±1.4^{A}	23.6±4.1^{A}	1007.4±190.1^{A}
1000	12.9±2.2^{A}	9.0±1.1^{A}	54.4±12.3^{A}	61.4±8.1^{A}	14.3±1.7^{A}	24.3±3.9^{A}	1167.2±377.0^{A}

Values expressed as Mean ± SD. Means within respective treatments followed by similar upper case letters are not significantly different at $\rho \leq 0.05$. Hb-Hemoglobin, RBC-Red Blood Cells, PCV-Packed Cell Volume, MCV-Mean Cell Volume, MCH-Mean Cell Hemoglobin, MCHC-Mean Cell Hemoglobin Concentration and PLT-Platelets.

4.6 Effects of a daily oral and intraperitoneal administration of the five aqueous plants extracts to mice for 28 days at high doses on white blood cell and differential white blood cell count

Table 4.38 and 4.39 shows the effects of a daily oral and intraperitoneal administration of aqueous extracts of *C. dependens* to mice for 28 days at 450, 670 and 1000 mg/kg body weight on white blood cells and differential white blood cell count. Results indicate that oral administration of aqueous extracts of C. dependens to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight caused similar effects to the levels of LYM ($\rho > 0.05$) which were significantly higher than those of the normal control mice group ($\rho < 0.05$). Extract-treated mice groups at 450, 670 and 1000 mg/kg body weight caused similar effects to the levels of NEU ($\rho > 0.05$). Extract-treated mice group at 450 mg/kg body weight caused a non-significant effect to the level of NEU relative to the normal control mice group ($\rho > 0.05$) (Table 4.38).

Table 4.38: Effects of a daily oral administration of aqueous extracts of *C. dependens* in mice for four weeks at high doses on white blood cells and differential white blood cell count

Treatment	White Blood Cell Count and Differential White Blood Cell Count					
	WBC ($x10^9$/L)	**NEU ($x10^9$/L)**	**LYM ($x10^9$/L)**	**EOS ($x10^9$/L)**	**MON ($x10^9$/L)**	**BAS ($x10^9$/L)**
Chasmanthera dependens (mg/kg body weight)						
Control	10.2 ± 3.0^{A}	3.1 ± 0.6^{B}	5.3 ± 1.1^{A}	1.0 ± 1.1^{A}	$0.8\pm0 .5^{B}$	0.1 ± 0.6^{A}
450	11.1 ± 3.5^{A}	3.1 ± 1.5^{AB}	6.1 ± 1.3^{B}	1.0 ± 0.5^{A}	0.8 ± 0.8^{B}	0.1 ± 0.5^{A}
670	13.6 ± 3.2^{A}	3.8 ± 0.8^{A}	7.4 ± 0.7^{B}	1.4 ± 0.8^{A}	1.1 ± 0.7^{B}	0.1 ± 0.7^{A}
1000	12.7 ± 2.8^{A}	3.6 ± 0.8^{A}	7.2 ± 0.6^{B}	0.8 ± 0.6^{A}	1.1 ± 0.6^{B}	0.2 ± 0.6^{A}

Results expressed as Mean ± SD. Values followed by the same superscript are not significantly different at $\rho \leq 0.05$. WBC = white blood cells; NEU = neutrophils; LYM = lymphocytes; MON = monocytes; EOS = eosinophils; BAS = basophils.

Intraperitoneal administration of aqueous extracts of *C. dependens* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight caused similar effects to the level of NEU and LYM at the three extract tested doses ($\rho > 0.05$) which was significantly lower relative to that of the normal control mice group ($\rho < 0.05$). Extract-treated mice groups at 450, 670 and 1000 mg/kg body weight caused similar effects to the levels of WBC, MON, EOS and BAS which were comparable to those for normal control mice group($p > 0.05$) (Table 4.39).

Table 4.39: Effects of daily intraperitoneal administration of aqueous extracts of *C. dependens* in mice for four weeks at high doses on white blood cell and differential white blood cell count

	White Blood Cell and Differential White Blood Cell Count					
Treatment	**WBC ($x10^9$/L)**	**NEU ($x10^9$/L)**	**LYM ($x10^9$/L)**	**EOS ($x10^9$/L)**	**MON ($x10^9$/L)**	**BAS ($x10^9$/L)**
Chasmanthera dependens (mg/kg body weight)						
Control	13.2 ± 1.1^{A}	4.1 ± 0.8^{B}	6.7 ± 0.8^{A}	1.2 ± 0.8^{A}	1.0 ± 0.6^{A}	0.2 ± 0.5^{A}
450	9.8 ± 4.2^{A}	2.7 ± 1.5^{A}	5.4 ± 1.9^{B}	0.9 ± 0.9^{A}	0.7 ± 0.8^{A}	0.1 ± 0.5^{A}
670	13.6 ± 3.2^{A}	3.8 ± 0.8^{A}	7.5 ± 1.7^{B}	1.3 ± 1.0^{A}	1.0 ± 1.3^{A}	0.1 ± 0.5^{A}
1000	14.5 ± 4.1^{A}	3.9 ± 1.3^{A}	8.2 ± 0.8^{B}	1.2 ± 0.8^{A}	1.0 ± 0.5^{A}	0.1 ± 0.5^{A}

Results expressed as Mean ± SD. Values followed by the same superscript are not significantly different at $\rho \leq 0.05$. WBC = white blood cells; NEU = neutrophils; LYM = lymphocytes; MON = monocytes; EOS = eosinophils; BAS = basophils.

Oral administration of aqueous extracts of *Mayrtenus undata* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight caused a non-significant effect on the levels of WBC, and MON at the three tested extract doses which were significantly lower than those of the normal control mice group.. Extract-treated mice groups at 450 and 670 mg/kg body weight caused similar effects to the levels of BAS ($\rho > 0.05$) which were significantly higher than those of the normal control mice group ($\rho < 0.05$). Extract-treated mice groups at 450, 670 and 1000 mg/kg body weight caused similar effects to the levels of BAS ($\rho > 0.05$). Extract-treated mice group at 1000 mg/kg body weight caused similar effects to the levels of BAS which were comparable to those of the normal control mice group ($p > 0.05$). Extract-treated mice groups at 450, 670 and 1000 mg/kg caused a non-significant effect to the levels of NEU, LYM and EOS which were comparable to those of the normal mice group ($\rho > 0.05$) (Table 4.40).

Table 4.40: Effects of a daily oral administration of aqueous extracts of *M. undata* in mice for four weeks at high doses on white blood cell and differential white blood cell count

	White Blood Cell and Differential White Blood Cell Count					
Treatment	**WBC ($x10^9$/L)**	**NEU ($x10^9$/L)**	**LYM ($x10^9$/L)**	**EOS ($x10^9$/L)**	**MON ($x10^9$/L)**	**BAS ($x10^9$/L)**
Mayrtenus undata (mg/kg body weight)						
Control	10.2 ± 3.0^{B}	3.1 ± 0.6^{A}	5.3 ± 1.1^{A}	1.0 ± 1.1^{A}	0.8 ± 0.5^{B}	$0.1\pm0 .6^{A}$
450	8.9 ± 1.0^{A}	2.7 ± 1.6^{A}	5.4 ± 1.0^{A}	0.0 ± 0.0^{A}	0.1 ± 0.0^{A}	0.8 ± 0.4^{B}
670	8.6 ± 4.8^{A}	3.2 ± 3.0^{A}	4.4 ± 1.8^{A}	0.0 ± 0.0^{A}	0.2 ± 0.1^{A}	0.8 ± 0.7^{B}
1000	7.8 ± 3.0^{A}	1.2 ± 1.0^{A}	6.2 ± 2.4^{A}	0.0 ± 0.0^{A}	0.1 ± 0.1^{A}	0.3 ± 0.2^{AB}

Results expressed as Mean ± SD. Values followed by the same superscript are not significantly different at $\rho \leq 0.05$. WBC = white blood cells; NEU = neutrophils; LYM = lymphocytes; MON = monocytes; EOS = eosinophils; BAS = basophils.

Intraperitoneal administration of aqueous extracts of *M. undata* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight caused similar effects to the levels of WBC at 450 and 1000 mg/kg body weight ($\rho > 0.05$) which are significantly lower than those of the normal control mice group ($\rho < 0.05$). Extract-treated mice group at 450 mg/kg body weight caused a significantly lower levels of WBC compared to the extract-treated mice groups at 670 mg/kg body weight ($\rho < 0.05$). Extract-treated mice group at 670 and 1000 mg/kg body weight caused similar effects to the levels of WBC ($\rho > 0.05$). Extract-treated mice group at 670 mg/kg body weight caused a non-significant effect to the levels of WBC relative to that of the normal control mice group ($\rho > 0.05$). Extract-treated mice groups at 450, 670 and 1000 mg/kg body weight caused similar effects to the levels of MON ($\rho > 0.05$) which were significantly lower relative to those of the normal control mice group ($\rho < 0.05$). Extract-treated mice groups at 450 and 670 mg/kg body weight caused a non-significant effect to the levels of BAS ($\rho > 0.05$) which was significantly lower than those of the normal control mice group ($\rho < 0.05$). Extract-treated mice groups at 450, 670 and 1000 mg/kg body weight caused similar effects to the levels of BAS ($\rho > 0.05$). Extract-treated mice group at 1000 mg/kg body weight caused a non-significant effect to the levels of BAS relative to that of the normal control mice group ($\rho > 0.05$). Extract-treated mice groups at 450, 670 and 1000 mg/kg body weight caused a non-significant effect to the levels of NEU, LYM and EOS which were comparable to those of the normal control mice group ($p > 0.05$) (Table 4.41).

Table 4.41: Effects of daily intraperitoneal administration of aqueous extracts of *M. undata* in mice for four weeks at high doses on White Blood Cells and differential white blood cell count

	White Blood Cell and Differential White Blood Cell Count					
Treatment	**WBC ($x10^9$/L)**	**NEU ($x10^9$/L)**	**LYM ($x10^9$/L)**	**EOS ($x10^9$/L)**	**MON ($x10^9$/L)**	**BAS ($x10^9$/L)**
Mayrtenus undata (mg/kg body weight)						
Control	13.2 ± 1.1^{C}	4.1 ± 0.8^{A}	6.7 ± 0.8^{A}	1.2 ± 0.8^{A}	1.0 ± 0.6^{B}	0.2 ± 0.5^{A}
450	6.0 ± 2.6^{A}	2.2 ± 1.0^{A}	3.0 ± 1.5^{A}	0.0 ± 0.0^{A}	0.1 ± 0.0^{A}	0.6 ± 0.5^{B}
670	12.6 ± 5.4^{BC}	4.9 ± 3.3^{A}	6.4 ± 2.3^{A}	$0.0\pm.0.1^{A}$	0.1 ± 0.1^{A}	1.2 ± 1.2^{B}
1000	9.0 ± 2.5^{AB}	1.4 ± 1.0^{A}	7.1 ± 3.6^{A}	0.0 ± 0.0^{A}	0.1 ± 0.1^{A}	0.4 ± 0.3^{AB}

Results expressed as Mean ± SD. Values followed by the same superscript are not significantly different at $\rho \leq 0.05$. WBC = white blood cells; NEU = neutrophils; LYM = lymphocytes; MON = monocytes; EOS = eosinophils; BAS = basophils.

Oral administration of aqueous extracts of *Syzigium cordutum* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight caused similar effects to the levels of WBC, LYM, MON, EOS and BAS which were comparable to that of the normal control mice group. Extract-treated mice groups at 450 mg/kg body weight caused a significant reduction in the level of NEU relative to that of the normal control group. Extract-treated mice groups at 450, 670 and 1000 mg/kg body weight caused similar effects to the levels of NEU. Extract-treated mice groups at 670 and 1000 mg/kg body weight caused similar effects to the levels of NEU which were comparable to those of the normal control mice group ($p > 0.05$) (Table 4.42).

Table 4.42: Effects of daily oral administration of aqueous extracts of *S. cordutum* in mice for four weeks on white blood cells and differential white blood cell count

Treatment	WBC ($x10^9$/L)	NEU ($x10^9$/L)	LYM ($x10^9$/L)	EOS ($x10^3$/L)	MON ($x10^9$/L)	BAS ($x10^9$/L)
Syzigium cordutum (mg/kg body weight)						
Control	10.2 ± 3.0^{A}	3.1 ± 0.6^{B}	5.3 ± 1.1^{A}	1.0 ± 0.1^{A}	0.8 ± 0.5^{A}	$0.1\pm0 .6^{A}$
450	9.1 ± 3.5^{A}	0.5 ± 0.2^{A}	6.7 ± 2.3^{A}	0.0 ± 0.0^{A}	2.0 ± 1.5^{A}	0.0 ± 0.0^{A}
670	10.8 ± 3.8^{A}	1.0 ± 0.4^{AB}	8.0 ± 2.9^{A}	0.0 ± 0.0^{A}	1.7 ± 0.7^{A}	0.0 ± 0.0^{A}
1000	11.9 ± 3.1^{A}	1.5 ± 0.8^{AB}	8.9 ± 1.9^{A}	0.0 ± 0.0^{A}	1.4 ± 0.9^{A}	0.0 ± 0.0^{A}

Results expressed as Mean ± SD. Values followed by the same superscript are not significantly different at $\rho \leq 0.05$. WBC = white blood cells; NEU = neutrophils; LYM = lymphocytes; MON = monocytes; EOS = eosinophils; BAS = basophils.

Intraperitoneal administration of aqueous extracts of *S. cordutum* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight caused similar effects to the levels of MON, EOS and BAS which were comparable to those of the normal control mice group ($\rho > 0.05$). Extract-treated mice groups at 450, 670 and 1000 mg/kg body weight caused similar effects to the levels of WBC and NEU ($\rho > 0.05$) which were significantly lower than those of the normal control mice group ($\rho < 0.05$). Extract-treated mice groups at 670 and 1000 mg/kg body weight caused similar effects to the levels of LYM ($\rho > 0.05$) Extract-treated mice group at 450 mg/kg body weight caused a non-significant effect to the levels of LYM when compared to the normal control mice group ($\rho > 0.05$) (Table 4.43).

Table 4.43: Effects of daily intraperitoneal administration of aqueous extracts of *Syzigium cordutum* in mice for four weeks on white blood cell and differential white blood cell count

Treatment	White Blood Cell and Differential White Blood Cell Count					
	WBC ($x10^9$/L)	**NEU ($x10^9$/L)**	**LYM ($x10^9$/L)**	**EOS ($x10^9$/L)**	**MON ($x10^9$/L)**	**BAS ($x10^9$/L)**
Syzigium cordutum (mg/kg body weight)						
Control	13.2 ± 1.1^{B}	4.1 ± 0.8^{B}	6.7 ± 0.8^{B}	1.2 ± 0.8^{A}	1.0 ± 0.6^{A}	0.2 ± 0.5^{A}
450	6.8 ± 1.3^{A}	0.5 ± 0.4^{A}	5.3 ± 0.9^{B}	0.0 ± 0.0^{A}	1.1 ± 0.3^{A}	0.0 ± 0.0^{A}
670	8.9 ± 3.7^{A}	1.5 ± 0.8^{A}	3.9 ± 1.2^{A}	0.0 ± 0.0^{A}	1.8 ± 0.5^{A}	0.0 ± 0.0^{A}
1000	9.2 ± 3.4^{A}	1.8 ± 0.8^{A}	6.2 ± 2.9^{AB}	0.0 ± 0.0^{A}	1.3 ± 0.4^{A}	0.0 ± 0.0^{A}

Results expressed as Mean ± SD. Values followed by the same superscript are not significantly different at $\rho \leq 0.05$. WBC = white blood cells; NEU = neutrophils; LYM = lymphocytes; MON = monocytes; EOS = eosinophils; BAS = basophils.

Oral administration of aqueous extracts of *M. subcordata* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight caused similar effects to the levels of EOS and BAS which were comparable to those of the normal control mice group. Extract-treated mice groups at 450, 670 and 1000 mg/kg body weight caused similar effects to the levels of NEU, LYM and MON ($\rho > 0.05$) which were significantly lower than those of the normal control mice group ($\rho < 0.05$). Extract-treated mice group at 450 and 670 mg/kg body weight caused similar effects to the level of WBC ($\rho > 0.05$) which were significantly lower than that of the normal control mice group ($\rho < 0.05$). Extract-treated mice group at 450 mg/kg body weight caused a significantly lower reduction to the level of WBC compared to that caused by the extract-treated mice group at 1000 mg/kg body weight. Extract-treated mice groups at 670 and 1000 mg/kg body weight caused similar effects to the level of WBC ($\rho > 0.05$) which was significantly lower than that of the normal control mice group ($\rho < 0.05$) (Table 4.43).

Table 4.44: Effects of a daily oral administration of aqueous extracts of *M. subcordata* in mice for four weeks at high doses on white blood cell and differential white blood cell count

Treatment	White Blood Cell and Differential White Blood Cell Count					
	WBC ($x10^9$/L)	**NEU ($x10^9$/L)**	**LYM ($x10^9$/L)**	**EOS ($x10^9$/L)**	**MON ($x10^9$/L)**	**BAS ($x10^9$/L)**
Maerua subcordata (mg/kg body weight)						
Control	18.3 ± 3.4^{C}	2.9 ± 0.7^{A}	12.1 ± 1.5^{B}	0.0 ± 0.0^{A}	2.9 ± 1.1^{B}	0.0 ± 0.0^{A}
450	14.6 ± 2.9^{BC}	7.1 ± 2.7^{B}	7.1 ± 2.2^{A}	0.1 ± 0.0^{A}	0.3 ± 0.2^{A}	0.0 ± 0.0^{A}
670	12.1 ± 2.6^{AB}	5.4 ± 2.4^{B}	6.5 ± 2.1^{A}	$0.1\pm.0.1^{A}$	0.2 ± 0.2^{A}	0.0 ± 0.0^{A}
1000	8.6 ± 2.3^{A}	3.5 ± 1.6^{B}	5.4 ± 1.3^{A}	0.1 ± 0.1^{A}	0.2 ± 0.1^{A}	0.0 ± 0.0^{A}

Results expressed as Mean ± SD. Values followed by the same superscript are not significantly different at $\rho \leq 0.05$. WBC = White Blood Cells; NEU = Neutrophils; LYM = Lymphocytes; MON = Monocytes; EOS = Eosinophils; BAS = Basophils.

Intraperitoneal administration of aqueous extracts of *M. subcordata* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight caused similar effects to the level of BAS which was comparable to that of the normal control mice group ($\rho > 0.05$). Extract-treated mice groups at 450, 670 and 1000 mg/kg body weight caused similar effects to the levels of WBC, LYM and MON ($\rho > 0.05$) which were significantly lower than those of the normal control mice group ($\rho < 0.05$). Extract-treated mice groups at 450, 670 and 1000 mg/kg body weight caused similar effects to the level of NEU ($\rho > 0.05$) which were significantly higher than those of the normal control mice group ($\rho < 0.05$). Extract-treated mice groups at 450 mg/kg body weight caused a significant increase in the level of EOS relative to that of the normal control mice group ($\rho < 0.05$). Extract treated mice groups at 670 and 1000 mg/kg body weight caused similar effects to the level of EOS which were comparable to that of the normal control mice group ($\rho > 0.05$) (Table 4.45).

Table 4.45: Effects of a daily intraperitoneal administration of aqueous extracts of *M. subcordata* in mice for four weeks at high doses on white blood cell and differential white blood cell count

Treatment	White Blood Cell and Differential White Blood Cell Count					
	WBC ($x10^9$/L)	**NEU ($x10^9$/L)**	**LYM ($x10^9$/L)**	**EOS ($x10^9$/L)**	**MON ($x10^9$/L)**	**BAS ($x10^9$/L)**
Maerua subcordata (mg/kg body weight)						
Control	16.7 ± 3.7^{B}	2.3 ± 0.7^{A}	11.3 ± 1.8^{B}	0.0 ± 0.0^{A}	2.7 ± 1.1^{B}	0.0 ± 0.0^{A}
450	11.3 ± 1.0^{A}	3.8 ± 1.9^{B}	6.2 ± 1.3^{A}	0.4 ± 0.2^{B}	0.5 ± 0.2^{A}	0.2 ± 0.2^{A}
670	11.0 ± 2.5^{A}	3.6 ± 1.9^{B}	7.4 ± 1.2^{A}	0.0 ± 0.0^{A}	0.2 ± 0.2^{A}	0.0 ± 0.0^{A}
1000	8.5 ± 2.8^{A}	2.7 ± 3.9^{AB}	5.8 ± 1.8^{A}	0.0 ± 0.0^{A}	0.1 ± 0.1^{A}	0.0 ± 0.0^{A}

Results expressed as Mean ± SD. Values followed by the same superscript are not significantly different at $\rho \leq 0.05$. WBC = White Blood Cells; NEU = Neutrophils; LYM = Lymphocytes; MON = Monocytes; EOS = Eosinophils; BAS = Basophils.

Oral administration of aqueous extracts of *Pappea capensis* to mice daily for 28 days at 450, 670 and 1000mg/kg body weight caused similar effects to the levels of MON, EOS and BAS which were comparable to those of the normal control mice group ($\rho > 0.05$). Extract-treated mice groups at 450, 670 and 1000 mg/kg body weight caused similar effects to the levels of WBC and LYM ($\rho > 0.05$) which were lower than those of the normal control mice group ($\rho < 0.05$). Extract-treated mice groups at 670 mg/kg body weight caused a significant increase in the level of NEU compared to that of the normal control mice group ($\rho < 0.05$). Extract-treated mice groups at 450 and 1000 mg/kg body weight caused similar effects to the level of NEU which were comparable to those of the normal control mice group ($\rho > 0.05$). Extract-treated mice group at 450 and 670 mg/kg body weight caused a similar effect to the levels of NEU ($p > 0.05$) (Table 4.46).

Table 4.46: Effects of a daily oral administration of aqueous extracts of *P. capensis* in mice for four weeks at high doses on white blood cell and differential white blood cell count

Treatment	White Blood Cell and Differential White Blood Cell Count					
	WBC ($x10^9$/L)	**NEU ($x10^9$/L)**	**LYM ($x10^9$/L)**	**EOS ($x10^9$/L)**	**MON ($x10^9$/L)**	**BAS ($x10^9$/L)**
Pappea capensis (mg/kg body weight)						
Control	18.3 ± 3.4^{B}	2.9 ± 0.7^{A}	12.1 ± 1.5^{B}	0.0 ± 0.0^{A}	2.9 ± 1.1^{A}	0.0 ± 0.0^{A}
450	9.8 ± 1.7^{A}	2.7 ± 1.4^{AB}	4.9 ± 0.8^{A}	0.0 ± 0.0^{A}	2.2 ± 0.3^{A}	0.0 ± 0.0^{A}
670	11.3 ± 2.6^{A}	3.1 ± 0.3^{B}	5.9 ± 1.4^{A}	0.0 ± 0.0^{A}	2.2 ± 0.7^{A}	0.0 ± 0.0^{A}
1000	12.2 ± 1.7^{A}	2.3 ± 0.2^{A}	6.7 ± 1.2^{A}	0.0 ± 0.0^{A}	2.4 ± 0.7^{A}	0.0 ± 0.0^{A}

Results expressed as Mean ± SD. Values followed by the same superscript are not significantly different at $\rho \leq 0.05$. WBC = white blood cells; NEU = neutrophils; LYM = lymphocytes; MON = monocytes; EOS = eosinophils; BAS = basophils.

Intraperitoneal administration of aqueous extracts of *P. capensis* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight caused similar effects to the levels of MON, EOS and BAS which were comparable to those of the normal control mice group ($\rho > 0.05$). Extract-treated mice groups at 450, 670 and 1000 mg/kg body weight caused similar effects to the levels of WBC and LYM ($\rho > 0.05$) which were significantly lower than those of the normal control mice group ($\rho < 0.05$). Extract-treated mice group at 1000 mg/kg body weight caused a significant increase in the level of NEU compared to that of the normal control mice group ($\rho < 0.05$). Extract-treated mice group at 450 and 670 mg/kg body weight caused similar effects of on the levels of NEU which were comparable to those of the normal control mice group ($\rho > 0.05$). Extract-treated mice groups at 450, 670 and 1000 mg/kg body weight caused similar effects on the levels of NEU ($\rho > 0.05$) (Table 4.47).

Table 4.47: Effects of a daily intraperitoneal administration of aqueous extracts of *P. capensis* in mice for four weeks at high doses on white blood cell and differential white blood cell count

Treatment	White Blood Cell and Differential White Blood Cell Count					
	WBC ($x10^9$/L)	**NEU ($x10^9$/L)**	**LYM ($x10^9$/L)**	**EOS ($x10^9$/L)**	**MON ($x10^9$/L)**	**BAS ($x10^9$/L)**
Pappea capensis (mg/kg body weight)						
Control	16.7 ± 3.7^{B}	2.3 ± 0.7^{A}	11.3 ± 1.8^{B}	0.0 ± 0.0^{A}	2.7 ± 1.1^{A}	0.0 ± 0.0^{A}
450	10.2 ± 1.6^{A}	2.1 ± 1.2^{AB}	5.9 ± 0.6^{A}	0.0 ± 0.0^{A}	2.3 ± 0.4^{A}	0.0 ± 0.0^{A}
670	10.5 ± 1.8^{A}	2.4 ± 0.5^{AB}	6.1 ± 1.2^{A}	0.0 ± 0.0^{A}	2.0 ± 0.6^{A}	0.0 ± 0.0^{A}
1000	9.9 ± 2.2^{A}	2.5 ± 0.5^{B}	5.5 ± 1.8^{A}	0.0 ± 0.0^{A}	2.0 ± 0.4^{A}	0.0 ± 0.0^{A}

Results expressed as Mean ± SD. Values followed by the same superscript are not significantly different at $\rho \leq 0.05$. WBC = White Blood Cells; NEU = Neutrophils; LYM = Lymphocytes; MON = Monocytes; EOS = Eosinophils; BAS = Basophils.

4.7 Effects of a daily oral and intraperitoneal administration of the five aqueous plants extracts at high doses to mice for 28 days on biochemical parameters

The effects of oral and intraperitoneal administration of aqueous extracts of *C. dependens* at 450, 670 and 1000mg/kg body weight in mice daily for four weeks on the levels of some biochemical parameters is shown in Table 4.48 to Table 4.51. Results shows that oral administration of aqueous extracts of *C. dependens* to mice daily for 28 days at the three tested doses caused similar effects to the levels of UREA, CREAT, T-BIL, D-BIL, UA, TG, HDL-C, ALT, AST, ALP, γ-GT, LDH, and γ-AMY which were comparable to those of the normal control mice group ($\rho > 0.05$). Extract-treated mice groups at 450, 670 and 1000 mg/kg body weight caused similar effects to the levels of T-CHOL and LDL-C ($\rho > 0.05$) which were significantly higher than those of the normal control mice group ($\rho < 0.05$) (Table 4.48; Table 4.49).

Table 4.48: Effects of oral administration of aqueous extracts of *C. dependens* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight on biochemical markers of kidney and liver function

	Biochemical parameters								
Treatment	**UREA (mmol/L)**	**CREAT (µmol/L)**	**T-BIL (µmol/L)**	**D-BIL (µmol/L)**	**UA (µmol/L)**	**T-CHOL (mmol/L)**	**TG (mmol/L)**	**HDL-C (mmol/L)**	**LDL-C (mmol/L)**
***Chasmanthera dependens* (mg/kg body weight)**									
Control	4.4±0.4^{A}	27.8±2.2^{A}	27.8±2.2^{A}	4.2±2.0^{A}	9.2±1.7.^{A}	1.0±0.3^{A}	0.8±0.3^{A}	0.0±0.01^{A}	0.5±0.2^{A}
450	4.8±0.9^{A}	36.4±9.2^{A}	7.8±2.5^{A}	4.6±1.5^{A}	16.4±7.6^{A}	1.6±0.3^{B}	0.7±0.1^{A}	0.1±0.0^{A}	1.3±0.3^{B}
670	5.0±0.7^{A}	29.4±6.5^{A}	12.6±6.6^{A}	6.8±3.4^{A}	10.1±3.3^{A}	1.5±0.2^{B}	0.9±0.2^{A}	0.1±0.0^{A}	1.1±0.1^{B}
1000	4.2±0.8^{A}	26.5±8.4^{A}	11.3±2.9^{A}	6.2±1.3^{A}	10.2±3.2^{A}	1.5±0.3^{B}	0.7±0.1^{A}	0.0±0.0^{A}	1.2±0.3^{B}

Values expressed as Mean ± SD. Means within respective columns followed by similar upper case letters are not significantly different at $p \leq 0.05$. CREAT- Creatinine, T-BIL- Total bilirubin, D-BIL- Direct bilirubin, UA- Uric acid, CHOL- Cholesterol, TG- Triglycerides, HDL-C –HDL Cholesterol and LDL- C-LDL cholesterol.

Table 4.49: Effects of oral administration of aqueous extracts of *C. dependens* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight on biochemical markers of the liver and pancreas function

	Enzyme activity					
Treatment	**ALT(U/L)**	**AST (U/L)**	**ALP (U/L)**	**γ GT (U/L)**	**LDH (U/L)**	**α-AMY(U/L)**
***Chasmanthera dependens* (mg/kg body weight)**						
Control	55.6±32.3^{A}	257.6±123.8^{A}	3.2±3.0^{A}	1.6±0.6^{A}	1038.8±516.2^{A}	347.0±97.5^{A}
450	55.0±6.2^{A}	288.0±119.1^{A}	4.0±2.0^{A}	0.6±0.9^{A}	1349.8±805.5^{A}	549.6±231.9^{A}
670	85.8±31.3^{A}	278.6±83.4^{A}	3.2±1.3^{A}	1.6±1.3^{A}	1698.8±527.5^{A}	648.4±256.3^{A}
1000	49.3±16.1^{A}	213.3±39.5^{A}	2.5±3.0^{A}	2.3±1.0^{A}	1038.8±516.2^{A}	427.0±84.2^{A}

Values expressed as Mean ± SD. Means within respective columns followed by similar upper case letters are not significantly different at $p \leq 0.05$. ALT-Alanine aminotransferase, AST-Aspartate aminotransferase, ALP-Alkaline phosphatase, γ-GT-gamma glutamyltransferase, LDH-Lactate dehydrogenase and α-AMY-alpha Amylase.

Intraperitoneal administration of aqueous extracts of *C. dependens* to mice daily for four weeks at 450, 670 and 1000 mg/kg body weight caused similar effects to the levels of UREA, CREAT, T-BIL, UA, TG, HDL-C, LDL-C, AST, ALP, γ-GT, LDH, and γ-AMY which were comparable to those of the normal control mice group. Extract-treated mice group at 1000 mg/kg body weight caused a significant increase in the level of ALT and D-BIL compared to that of the normal control mice group ($\rho < 0.05$). Extract-treated mice groups at 450, and 670 mg/kg body weight caused similar effects to the level of ALT and D-BIL which were comparable to those of the normal control mice group ($\rho > 0.05$). Extract-treated mice groups at 450 and 670 mg/kg body weight caused similar effects to the level of ALT and D-BIL ($\rho > 0.05$) which were significantly lower than those of the extract-treated mice group at 1000 mg/kg body weight ($\rho < 0.05$) (Table 4.50; Table 4.51).

Table 4.50: Effects of intraperitoneal administration of aqueous extracts of *C. dependens* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight on biochemical markers of kidney and liver function

	Biochemical parameters								
Treatment	**UREA (mmol/L)**	**CREAT (µmol/L)**	**T-BIL (µmol/L)**	**D-BIL (µmol/L)**	**UA (µmol/L)**	**T-CHOL (mmol/L)**	**TG (mmol/L)**	**HDL-C (mmol/L)**	**LDL-C (mmol/L)**
***Chasmanthera dependens* (mg/kg body weight)**									
Control	5.4 ± 2.1^{A}	21.8 ± 7.6^{A}	10.9 ± 3.8^{A}	5.4 ± 1.7^{A}	5.2 ± 1.6^{A}	3.6 ± 1.7^{A}	1.2 ± 0.2^{A}	0.6 ± 0.2^{A}	0.5 ± 0.1^{A}
450	4.0 ± 1.0^{A}	28.6 ± 6.0^{A}	9.3 ± 2.1^{A}	5.3 ± 1.1^{A}	6.0 ± 1.2^{A}	2.8 ± 1.5^{A}	1.2 ± 0.3^{A}	0.7 ± 0.1^{A}	0.6 ± 0.0^{A}
670	4.1 ± 1.8^{A}	31.4 ± 5.7^{A}	9.8 ± 3.2^{A}	5.8 ± 1.4^{A}	6.0 ± 2.1^{A}	2.8 ± 0.5^{A}	1.5 ± 0.3^{A}	0.7 ± 0.3^{A}	0.6 ± 0.1^{A}
1000	6.3 ± 1.9^{A}	26.4 ± 3.4^{A}	15.3 ± 2.9^{A}	9.0 ± 2.2^{B}	6.7 ± 2.9^{A}	2.0 ± 1.4^{A}	1.3 ± 0.3^{A}	0.8 ± 0.1^{A}	0.6 ± 0.1^{A}

Values expressed as Mean ± SD. Means within respective columns followed by similar upper case letters are not significantly different at $p \leq 0.05$. CREAT- Creatinine, T-BIL-Total bilirubin, D-BIL- Direct bilirubin, UA- Uric acid, CHOL-Cholesterol, TG- Triglycerides, HDL-C –HDL Cholesterol and LDL- C-LDL cholesterol.

Table 4.51: Effects of intraperitoneal administration of aqueous extracts of *C. dependens* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight on biochemical markers of liver and pancreas function

	Enzyme activity					
Treatment	**ALT (U/L)**	**AST (U/L)**	**ALP (U/L)**	**γ GT (U/L)**	**LDH (U/L)**	**α AMY (U/L)**
***Chasmanthera dependens* (mg/kg body weight)**						
Control	40.8 ± 15.4^{A}	40.8 ± 15.4^{A}	242.2 ± 71.3^{A}	4.0 ± 2.0^{A}	95.8 ± 33.7^{A}	1648.6 ± 237.3^{A}
450	54.6 ± 21^{A}	68.2 ± 26.7^{A}	288.6 ± 62.0^{A}	3.4 ± 3.1^{A}	109.2 ± 24.0^{A}	1161.0 ± 566.3^{A}
670	67.7 ± 16.7^{A}	84.6 ± 30.6^{A}	328.0 ± 115.6^{A}	3.0 ± 1.9^{A}	112.2 ± 46.1^{A}	1373.0 ± 639.9^{A}
1000	79.2 ± 16.2^{B}	99.0 ± 57.0^{A}	418.8 ± 187.0^{A}	1.0 ± 0.7^{A}	103.2 ± 58.1^{A}	1589.0 ± 450.3^{A}

Values expressed as Mean ± SD. Means within respective columns followed by similar upper case letters are not significantly different at $p \leq 0.05$. ALT-Alanine aminotransferase, AST-Aspartate aminotransferase, ALP-Alkaline phosphatase, γ-GT-gamma glutamyltransferase, LDH-Lactate dehydrogenase and α-AMY-alpha Amylase.

The effects of oral and intraperitoneal administration of aqueous extracts of *M. undata* to mice daily for four weeks at 450, 670 and 1000mg/kg body weight on some biochemical analytes is shown in Tables 4.52 to Table 4.55. Results shows that oral administration of aqueous extracts of *M. undata* to mice daily for four weeks at the three tested doses caused similar effects to the levels of CREAT, T-BIL, D-BIL, TG, LDL-C, ALT, ALP, GGT, LDH and AMY which was comparable to that of the normal control mice group ($\rho > 0.05$). Extract-treated mice group at 450, 670 and 1000 mg/kg body weight caused similar effects to the level of HDL-C ($\rho > 0.05$) which was significantly higher than that of the normal control mice group ($\rho < 0.05$).

Extract-treated mice group at 450, 670 and 1000 mg/kg body weight caused similar effects to the levels of T-CHOL and AST ($\rho > 0.05$) which were significantly higher than those of the normal control mice group ($\rho < 0.05$). Extract-treated mice group at 450 mg/kg body weight caused similar effect to the levels of T-CHOL and AST compared to that of the normal control mice group ($\rho > 0.05$).

Extract-treated mice groups at 450 and 670 mg/kg body weight caused similar effects to the level of UA which was comparable to that of the normal control mice group ($\rho > 0.05$). Extract-treated mice groups at 670 and 1000 mg/kg body weight caused similar effects to the level of UA ($\rho > 0.05$). Extract-treated mice at 1000 mg/kg body weight caused a significantly lower than that of the normal control mice group ($\rho < 0.05$).

Extract-treated mice groups at 450 and 670 mg/kg body weight caused similar effects to the levels of UREA ($\rho > 0.05$) which were significantly higher than those of the normal control mice group ($\rho < 0.05$). Extract-treated mice groups at 450 and 670 mg/kg body weight caused similar effects to the level of UREA ($\rho > 0.05$) which were significantly lower than those of the extract-treated mice group at 1000 mg/kg body weight ($\rho < 0.05$). Extract-treated mice group at 450 mg/kg body weight caused similar effects to the levels UREA compared to that of the normal control mice group ($\rho > 0.05$). Extract-treated mice group at 1000 mg/kg body weight caused a significant increase in the level of UREA compared to that of the normal control mice group ($\rho < 0.05$) (Table 4.52 and 4.53).

Table 4.52: Effects of oral administration of aqueous extracts of *M. undata* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight on biochemical markers of kidney and liver function

Treatment	Biochemical parameters								
	UREA (mmol/L)	CREAT (µmol/L)	T-BIL (µmol/L)	D-BIL (µmol/L)	UA (µmol/L)	T-CHOL (mmol/L)	TG (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)
***Mayrtenus undata* (mg/kg body weight)**									
Control	4.4 ± 0.4^{A}	27.8 ± 2.2^{A}	8.0 ± 3.9^{A}	4.2 ± 2.0^{A}	9.2 ± 1.7^{B}	1.0 ± 0.3^{A}	0.8 ± 0.3^{A}	0.0 ± 0.0^{A}	0.5 ± 0.1^{A}
450	4.7 ± 1.0^{AB}	25.0 ± 14.2^{A}	11.1 ± 7.0^{A}	4.6 ± 2.5^{A}	10.7 ± 5.2^{B}	1.3 ± 0.2^{AB}	0.6 ± 0.2^{A}	0.7 ± 0.2^{B}	0.5 ± 0.1^{A}
670	6.3 ± 0.8^{BC}	15.4 ± 4.1^{A}	11.7 ± 5.6^{A}	6.0 ± 4.6^{A}	7.0 ± 4.8^{AB}	1.6 ± 0.3^{B}	0.9 ± 0.1^{A}	0.9 ± 0.2^{B}	0.4 ± 0.1^{A}
1000	6.1 ± 0.8^{C}	14.4 ± 8.3^{A}	7.9 ± 4.4^{A}	3.1 ± 1.1^{A}	2.2 ± 0.7^{A}	1.5 ± 0.4^{B}	0.8 ± 0.3^{A}	0.6 ± 0.2^{B}	0.5 ± 0.1^{A}

Values expressed as Mean ± SD. Means within respective columns followed by similar upper case letters are not significantly different at $p \leq 0.05$. CREAT = Creatinine, T-BIL = Total bilirubin, D-BIL = Direct bilirubin, UA = Uric acid, CHOL = Cholesterol, TG = Triacylglycerol, HDL-C = HDL Cholesterol and LDL-C = LDL Cholesterol.

Table 4.53: Effects of oral administration of aqueous extracts of *M. undata* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight on biochemical markers of liver and pancreas function

	Enzyme activity					
Treatment	**ALT (U/L)**	**AST (U/L)**	**ALP (U/L)**	**γ-GT (U/L)**	**LDH (U/L)**	**α-AMY (U/L)**
Mayrtenus undata (mg/kg body weight)						
Control	55.6 ± 32.3^{A}	257.6 ± 123.8^{A}	3.2 ± 3.1^{A}	1.6 ± 0.6^{A}	1038.8 ± 516.2^{A}	347.0 ± 97.5^{A}
450	69.0 ± 48.8^{A}	459.8 ± 153.8^{AB}	6.4 ± 3.9^{A}	5.4 ± 2.4^{A}	1798.6 ± 499.0^{A}	855.8 ± 414.7^{A}
670	87.8 ± 22.8^{A}	600.6 ± 88.7^{B}	3.4 ± 2.1^{A}	5.2 ± 3.3^{A}	2032.4 ± 375.2^{A}	836.0 ± 522.2^{A}
1000	83.0 ± 61.8^{A}	521.2 ± 177.9^{B}	5.2 ± 4.4^{A}	7.4 ± 1.5^{A}	1365.8 ± 768.7^{A}	839.4 ± 452.8^{A}

Values expressed as Mean ± SD. Means within respective columns followed by similar upper case letters are not significantly different at $p \leq 0.05$. ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, ALP = Alkaline phosphatase, γ-GT = gamma glutamyltransferase, LDH = Lactate dehydrogenase and α-AMY = alpha Amylase.

Intraperitoneal administration of aqueous extracts of *M. undata* to mice daily for four weeks at 450, 670 and mg/kg body weight caused similar effects to the levels of UREA, CREAT, T-BIL, D-BIL, T-CHOL, TG, HDL-C, LDL-C, GGT, LDH, and AMY which was comparable to that of the normal control mice group ($\rho > 0.05$).

Extract-treated mice groups at 670 and 1000 mg/kg body weight caused similar effects to the level of UA which was comparable to that of the normal control mice group ($\rho > 0.05$). Extract-treated mice groups at 450 and 1000 mg/kg body weight caused similar effects to the level of UA which was comparable to that of the normal control mice group ($\rho > 0.05$). Extract-treated mice group at 450 mg/kg body weight caused a significantly reduced level of UA compared to the extract-treated mice at 670 mg/kg body weight ($\rho < 0.05$).

Extract-treated mice groups at 450, 670 and 1000 mg/kg body weight caused similar effects to the level of ALT ($\rho > 0.05$) which was significantly lower than that of the normal control mice group ($\rho < 0.05$). Extract-treated mice groups at 670 and 1000 mg/kg body weight caused similar effects to the level of ALT which is comparable to those of the normal control mice group ($\rho > 0.05$).

Extract-treated mice groups at 670 mg/kg body weight caused a significant increase in the level of AST compared to that of the normal control mice group ($\rho < 0.05$). Extract-treated mice groups at 450 and 1000 mg/kg body weight caused similar effects to the level of AST which were comparable to that of the normal control mice group ($\rho >$

0.05). Extract-treated mice groups at 450, 670 and 1000 mg/kg body weight caused similar effects to the level of AST ($\rho > 0.05$).

Extract-treated mice groups at 450 and 1000 mg/kg body weight caused similar effects to the level of ALP ($\rho > 0.05$) which was significantly higher than that of the normal control mice group ($\rho < 0.05$). Extract-treated mice group at 450 mg/kg body weight caused a non-significant effect to the level of ALP compared to that of the normal control mice group ($\rho > 0.05$). Extract-treated mice group at 670 mg/kg body weight caused a significant increase in the level of ALP relative to that of the control mice group ($\rho < 0.05$). Extract-treated mice group at 450 and 1000 mg/kg body weight caused similar effects to the level of ALP ($\rho > 0.05$) which was significantly lower than that of the extract-treated mice group at 670 mg/kg body weight ($\rho < 0.05$) (Table 4.54:Table 4.55).

Table 4.54: Effects of intraperitoneal administration of aqueous extracts of *M. undata* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight on biochemical markers of kidney and liver function

Treatment	Biochemical parameters								
	UREA (mmol/L)	CREAT (µmol/L)	T-BIL (µmol/L)	D-BIL (µmol/L)	UA (µmol/L)	T-CHOL (mmol/L)	TG (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)
Mayrtenus undata (mg/kg body weight)									
Control	5.4±2.1^{A}	21.8±7.6^{A}	10.9±3.0^{A}	5.4±1.7^{A}	5.2±1.6^{AB}	3.6±1.7^{A}	1.2±0.16^{A}	0.6±0.2^{B}	0.5±0.1^{A}
450	6.8±4.4^{A}	25.2±17.5^{A}	6.8±1.3^{A}	3.5±0.4^{A}	3.4±1.1^{A}	6.8±6.7^{A}	1.1±0.40^{A}	0.6±0.3^{B}	0.5±0.1^{A}
670	3.4±1.3^{A}	22.0±11.1^{A}	10.0±3.1^{A}	3.9±0.3^{A}	4.9±0.9^{B}	4.2±1.5^{A}	1.6±0.43^{A}	0.7±0.1^{B}	0.4±0.1^{A}
1000	6.1±2.9^{A}	23.6±6.6^{A}	11.4±5.2^{A}	4.6±0.9^{A}	5.7±0.9^{AB}	2.0±1.2^{A}	1.6±0.34^{A}	1.0±0.3^{B}	0.5±0.2^{A}

Values expressed as Mean ± SD for five animals per group. Means within respective columns followed by similar upper case letters are not significantly different at $p \leq 0.05$. CREAT = Creatinine, T-BIL = Total bilirubin, D-BIL = Direct bilirubin, UA = Uric acid, CHOL = Cholesterol, TG = Triacylglycerol, HDL-C = HDL-Cholesterol and LDL-C = LDL-Cholesterol.

Table 4.55: Effects of intraperitoneal administration of aqueous extracts of *M. undata* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight on biochemical markers of liver and pancreas function

Treatment	Enzyme activity					
	ALT (U/L)	AST (U/L)	ALP (U/L)	γ-GT (U/L)	LDH (U/L)	α-AMY (U/L)
Mayrtenus undata (mg/kg body weight)						
Control	5.4±1.7^{B}	40.8±15.4^{A}	242.2±71.3^{A}	4.0±2.0^{A}	95.8±33.7^{A}	1648.6±237.3^{A}
450	4.6±0.9^{A}	62.8±28.5^{AB}	488.8±90.8^{AB}	5.6±9.2^{A}	65.6±13.5^{A}	1799.4±463.0^{A}
670	3.5±0.4^{AB}	116.8±31.6^{B}	866.6±330.7^{C}	3.4±2.1^{A}	117.0±21.7^{A}	2234.4±385.4^{A}
1000	3.9±0.3^{AB}	103.8±53.2^{AB}	694.2±189.5^{BC}	2.6±2.6^{A}	97.6±74.1^{A}	1874.0±534.0^{A}

Values expressed as Mean ± SD. Means within respective columns followed by similar upper case letters are not significantly different at $p \leq 0.05$. ALT-Alanine aminotransferase, AST- Aspartate aminotransferase, ALP- Alkaline phosphatase, γ GT-gamma glutamyltransferase, LDH- Lactate dehydrogenase and α AMY- alpha Amylase.

The effects of oral and intraperitoneal administration of aqueous extracts of *S. cordutum* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight on some blood analytes is shown in Table 4.56 to Table 4.59. Results show that oral administration of aqueous extracts of *S. cordutum* to mice daily for 28 days at the three tested doses caused similar effects in the levels of UREA, UA, T-CHOL, ALT, AST, ALP, GGT and LDH which was comparable to that of the normal control mice group ($\rho > 0.05$). Extract-treated mice groups at 450 and 670 mg/kg body weight caused similar effects to the level of α-AMY ($\rho > 0.05$) which was significantly higher than that of the normal control mice group ($\rho < 0.05$). Extract-treated mice groups at 450 and 670 mg/kg body weight caused similar effects to the level of α-AMY ($\rho > 0.05$) which were significantly higher than that of the extract-treated mice group at 1000 mg/kg body weight ($\rho < 0.05$). Extract-treated mice group at 1000 mg/kg body weight caused a non-significant effect to the level of α-AMY when compared to that of the normal control mice group ($\rho > 0.05$).

Extract-treated mice groups at 670 and 1000 mg/kg body weight caused similar effects to the level of CREAT which were comparable to those of normal control mice group ($\rho > 0.05$). Extract-treated mice group at 670 and 1000 mg/kg body weight caused similar effects to the level of CREAT ($\rho > 0.05$) which were significantly higher than those of the extract-treated mice at 450 mg/kg body weight ($\rho < 0.05$). Extract-treated mice group at b450 mg/kg body weight caused a significant decrease to the level of CREAT when compared to that of the normal control mice group ($\rho < 0.05$).

Extract-treated mice group at 670 and 1000 mg/kg body weight caused similar effects to the level of T-BIL ($\rho > 0.05$) which were significantly lower than those of the normal control mice group ($\rho < 0.05$). Extract-treated mice group at 670 and 1000 mg/kg body weight caused similar effects to the level of T-BIL ($\rho > 0.05$) which were significantly lower than that of the extract-treated mice group at 450 mg/kg body weight ($\rho < 0.05$). Extract-treated mice group at 450 mg/kg body weight caused a significant increase in the level of T-BIL relative to that of the normal control mice group ($\rho < 0.05$). Extract-treated mice groups at 670 and 1000mg/kg body weight caused similar effects to the level of D-BIL ($\rho > 0.05$) which were significantly lower ($\rho < 0.05$) than those of the normal control mice group and those of the extract-treated mice at 450 mg/kg body weight which were also similar ($\rho > 0.05$).

Extract-treated mice groups at 670 and 1000 mg/kg body weight caused similar effects to the level of TG which were comparable to that of the normal control mice group ($\rho > 0.05$). Extract-treated mice group at 450 mg/kg body weight caused a significant decrease in the level of TG compared to that of the normal control mice group ($\rho < 0.05$). Extract-treated mice groups at 450 and 670 mg/kg body weight caused similar effects to the level of TG ($\rho > 0.05$). Likewise, extracted mice groups at 670 and 1000 mg/kg body weight caused similar effects to the level of TG ($\rho > 0.05$). Extract-treated mice groups at 450, 670 and 1000 mg/kg body weight caused similar effects to the level of HDL-C ($\rho > 0.05$) which were significantly higher than that of the normal control mice group ($\rho < 0.05$). Extract-treated mice groups at 450 and 1000 mg/kg body weight caused similar effects to the level of LDL-C ($\rho > 0.05$) which were significantly lower

($\rho < 0.05$) than those of the normal control mice and extract-treated mice group at 670 mg/kg body weight which were also similar ($\rho > 0.05$) (Table 4.56; Table 4.57).

Table 4.56: Effects of oral administration of aqueous extracts of *S. cordutum* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight on biochemical markers of kidney and liver function

Treatment	Biochemical parameters								
	UREA (mmol/L)	CREAT (µmol/L)	T-BIL (µmol/L)	D-BIL (µmol/L)	UA (µmol/L)	T-CHOL (mmol/L)	TG (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)
Syzigium cordutum (mg/kg body weight)									
Control	4.4±0.4^{A}	27.8±2.2^{B}	8.0±3.9^{B}	4.2±2.0^{B}	9.2±1.7^{A}	1.0±0.3^{A}	0.8±0.3^{B}	0.0±0.0^{A}	0.5±0.2^{B}
450	3.5±1.1^{A}	10.6±4.3^{A}	13.9±3.6^{C}	5.2±2.2^{B}	10.2±2.7^{A}	0.9±0.2^{A}	0.3±0.1^{A}	0.5±0.1^{B}	0.3±0.2^{A}
670	3.6±0.6^{A}	36.2±10.0^{B}	1.7±0.4^{A}	0.6±0.2^{A}	12.4±5.8^{A}	1.1±0.3^{A}	0.7±0.2^{AB}	0.5±0.1^{B}	0.5±0.1^{B}
1000	4.8±1.9^{A}	41.3±11.5^{B}	1.1±0.6^{A}	0.5±0.3^{A}	9.7±4.7^{A}	1.3±0.1^{A}	0.8±0.3^{B}	0.4±0.1^{B}	0.3±0.1^{A}

Values expressed as Mean ± SD. Means within respective columns followed by similar upper case letters are not significantly different at $p \leq 0.05$. CREAT- Creatinine, T-BIL- Total bilirubin, D-BIL- Direct bilirubin, UA- Uric acid, CHOL- Cholesterol, TG- Triglycerides, HDL-C –HDL Cholesterol and LDL- C-LDL cholesterol.

Table 4.57: Effects of oral administration of aqueous extracts of *S. cordutum* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight on biochemical markers of liver and pancreas function

Treatment	Enzyme activity					
	ALT (U/L)	AST (U/L)	ALP (U/L)	γ-GT (U/L)	LDH (U/L)	α-AMY (U/L)
Syzigium cordutum (mg/kg body weight)						
Control	55.6±32.3^{A}	257.6±123.8^{AB}	3.2±3.1^{A}	1.6±0.6^{A}	1038.8±516.2^{A}	347.0±97.5^{A}
450	62.0±12.7^{A}	177.6±24.3^{A}	3.7±1.5^{A}	5.0±3.4^{A}	1752.6±347.8^{A}	795.8±304.3^{B}
670	79.4±44.1^{A}	165.6±60.1^{A}	2.5±2.7^{A}	5.0±2.3^{A}	2607.2±619.8^{A}	1044.6±91.2^{B}
1000	80.2±9.3^{A}	342.7±25.3^{A}	3.2±1.5^{A}	1.4±0.4^{A}	2774.2±570.9^{A}	330.0±81.5^{A}

Values expressed as Mean ± SD. Means within respective columns followed by similar upper case letters are not significantly different at $p \leq 0.05$. ALT-Alanine aminotransferase, AST- Aspartate aminotransferase, ALP- Alkaline phosphatase, γ GT- gamma glutamyltransferase, LDH- Lactate dehydrogenase and α AMY- alpha Amylase.

Intraperitoneal administration of aqueous extracts of *S. cordutum* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight caused similar effects to the levels of CREAT, T-BIL, UA,T-CHOL, TG, LDL-C, ALT and ALP which were comparable to that of the normal control mice group ($\rho > 0.05$).

Extract-treated mice groups at 450, 670 and 1000 mg/kg body weight caused similar effects to the levels of UREA and D-BIL ($\rho > 0.05$) which were significantly lower than those of the normal control mice group ($\rho < 0.05$).

Extract-treated mice groups at 450, 670 and 1000 mg/kg body weight caused a similar decrease in the level of HDL-C compared to that of the normal control mice group ($\rho < 0.05$).

Extract-treated mice groups at 670 and 1000 mg/kg body weight caused similar effects to the level of AST ($\rho > 0.05$) which was significantly higher than that of the normal control mice group ($\rho < 0.05$). Extract-treated mice group at 450 mg/kg body weight caused a non-significant effect on the level of AST compared to that of the normal control mice group ($\rho > 0.05$). Extract-treated mice groups at 450, 670 and 1000 mg/kg body weight caused similar effects to the level of AST ($\rho > 0.05$).

Extract-treated mice groups at 450, 670 and 1000 mg/kg body weight caused similar effects to the level of γ-GT which were comparable to those of the normal control mice group. Extract-treated mice groups at 670 mg/kg body weight caused a significant

decrease in the level of γ-GT relative to that of the normal control mice group. Extract-treated mice groups at 670 and 1000 mg/kg body weight caused similar effects to the level of γ-GT.

Extract-treated mice groups at 670 and 1000 mg/kg body weight caused similar effects to the level of LDH ($\rho > 0.05$) which were significantly higher than those of the normal control mice group ($\rho < 0.05$). Extract-treated mice group at 450 mg/kg body weight caused a non-significant effect to the level of LDH compared to that of the normal control mice group ($\rho > 0.05$). Extract-treated mice groups at 450, 670 and 1000 mg/kg body weight caused similar effects to the levels of LDH which were comparable to that of the normal control mice group ($\rho > 0.05$).

Extract-treated mice group at 670 and 1000 mg/kg body weight caused similar effects to the level of AMY which were comparable to that of the normal control mice group ($\rho > 0.05$). Extract-treated mice group at 450 mg/kg body weight caused a significant increase in the level of AMY compared to the normal control mice group ($\rho < 0.05$). Extract-treated mice groups at 670 and 1000 mg/kg body weight caused similar effects to the level of AMY ($\rho > 0.05$) which were significantly lower than that of the extract-treated mice group at 450 mg/kg body weight ($\rho < 0.05$) (Table 4.58; Table 4.59).

Table 4.58: Effects of intraperitoneal administration of aqueous extracts of *S. cordutum* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight on biochemical markers of kidney and liver function

Treatment	Biochemical parameters								
	UREA (mmol/L)	CREAT (µmol/L)	T-BIL (µmol/L)	D-BIL (µmol/L)	UA (µmol/L)	T-CHOL (mmol/L)	TG (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)
Syzigium cordutum (mg/kg body weight)									
Control	5.4±2.1^{B}	21.8±7.6^{A}	8.8±3.7^{A}	5.4±1.7^{B}	5.2±1.6^{A}	3.6±1.6^{A}	1.2±0.1^{A}	0.6±0.1^{A}	0.5±0.0^{B}
450	0.7±0.2^{A}	35.3±17.0^{A}	1.2±0.3^{A}	0.4±0.1^{A}	3.8±1.0^{A}	2.0±1.8^{A}	1.7±0.4^{A}	0.7±0.1^{B}	0.4±0.1^{B}
670	0.2±0.2^{A}	33.5±9.5^{A}	0.4±0.2^{A}	0.2±0.1^{A}	4.7±1.2^{A}	4.4±1.5^{A}	1.1±0.2^{A}	0.7±0.1^{B}	0.6±0.2^{B}
1000	0.7±0.4^{A}	33.4±7.4^{A}	1.5±0.6^{A}	0.7±0.3^{A}	4.4±1.9^{A}	3.0±1.5^{A}	1.0±0.3^{A}	0.7±0.2^{B}	0.5±0.1^{B}

Values expressed as Mean ± SD. Means within respective columns followed by similar upper case letters are not significantly different at $p \leq 0.05$. CREAT = Creatinine, T-BIL = Total bilirubin, D-BIL = Direct bilirubin, UA = Uric acid, CHOL = Cholesterol, TG = Triacylglycerols, HDL-C = HDL Cholesterol and LDL-C = LDL cholesterol.

Table 4.59: Effects of intraperitoneal administration of aqueous extracts of *S. cordutum* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight on biochemical markers of liver and pancreas function

Treatment	Enzyme activity					
	ALT (U/L)	AST (U/L)	ALP (U/L)	γ-GT (U/L)	LDH (U/L)	α-AMY (U/L)
Syzigium cordutum (mg/kg body weight)						
Control	5.4±1.7^{A}	40.8±15.4^{A}	242.2±71.3^{A}	4.0±2.0^{B}	95.8±33.7^{A}	1648.6±237.3^{A}
450	0.4±0.1^{A}	59.5±26.0^{AB}	298.9±89.6^{A}	4.0±3.0^{B}	108.8±27.9^{AB}	3060.4±197.0^{B}
670	0.2±0.1^{A}	77.4±23.8^{B}	214.6±54.9^{A}	1.9±1.4^{A}	141.8±37.0^{B}	2019.2±758.0^{A}
1000	0.7±0.3^{A}	84.6±34.3^{B}	310.9±60.0^{A}	2.3±1.9^{AB}	58.4±43.5^{B}	1744.0±331.0^{A}

Values expressed as Means ± SD for five animals per group. Means within respective columns followed by similar upper case letters are not significantly different at $p \leq 0.05$ by ANOVA and post ANOVA; ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, ALP = Alkaline phosphatase, γ-GT = gamma glutamyltransferase, LDH = Lactate dehydrogenase and α-AMY = alpha Amylase.

The effects of oral and intraperitoneal administration of aqueous extracts of *M. subcordata* at 450, 670 and 1000 mg/kg body weight in mice daily for four weeks on some blood analytes is shown in Table 4.60 to Table 4.63 respectively. Results show that oral administration of aqueous extracts of *M. subcordata* to mice daily for 28 days at the three tested doses resulted in a non-significant effect on the levels of UREA, CREAT, T-BIL, UA, T-CHOL, TG, LDL-C, ALT, AST, ALP, γ-GT and LDH which were comparable to that of the normal control mice group ($\rho > 0.05$).

Extract-treated mice groups at 450, and 1000 mg/kg body weight caused similar effects to the level of HDL-C which were comparable to that of the normal control mice group. Extract-treated mice group at 670 mg/kg body weight caused a significant increase in the level of HDL-C compared to that of the normal control mice group ($\rho < 0.05$). Extract-treated mice groups at 670 and 1000 mg/kg body weight caused similar effects to the level of HDL-C ($\rho > 0.05$).

Extract-treated mice groups at 450 and 670 mg/kg body weight caused similar effects to the level of γ-AMY which were significantly higher than that of the normal control mice group ($\rho < 0.05$). Extract-treated mice group at 1000 mg/kg body weight caused a non-significant effect to the level of γ-AMY compared to that of the normal control mice group ($\rho > 0.05$). Extract-treated mice groups at 450, 670 and 1000 mg/kg body weight caused similar effects to the level of γ-AMY ($\rho > 0.05$) (Table 4.60; Table 4.61).

Table 4.60: Effects of oral administration of aqueous extracts of *M. subcordata* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight on biochemical markers of kidney and liver function

Treatment	Biochemical parameters								
	UREA (mmol/L)	CREAT (µmol/L)	T-BIL (µmol/L)	D-BIL (µmol/L)	UA (µmol/L)	T-CHOL (mmol/L)	TG (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)
Maerua subcordata (mg/kg body weight)									
Control	5.4±1.6^{A}	55.1±12.6^{A}	12.9±9.1^{A}	0.5±0.4^{A}	12.4±4.3^{A}	0.9±0.5^{A}	1.3±1.1^{A}	0.3±0.1^{A}	0.6±0.2^{A}
450	5.9±1.9^{A}	52.3±30.4^{A}	7.3±2.7^{A}	3.3±1.3^{AB}	44.6±19.3^{A}	0.9±0.1^{A}	0.4±0.1^{A}	0.2±0.1^{A}	0.5±0.2^{A}
670	7.2±2.0^{A}	32.3±8.5^{A}	14.5±2.9^{A}	5.9±1.2^{BC}	98.9±10.6^{A}	1.3±0.2^{A}	0.4±0.1^{A}	0.8±0.2^{B}	0.5±0.2^{A}
1000	7.8±1.0^{A}	30.6±11.2^{A}	16.4±8.3^{A}	7.7±4.5^{C}	40.3±16.7^{A}	1.3±0.4^{A}	0.5±0.5^{A}	0.6±0.3^{AB}	0.7±0.2^{A}

Values expressed as Mean ± SD. Means within respective columns followed by similar upper case letters are not significantly different at $p \leq 0.05$. CREAT- Creatinine, T-BIL- Total bilirubin, D-BIL- Direct bilirubin, UA- Uric acid, CHOL- Cholesterol, TG- Triglycerides, HDL-C –HDL Cholesterol and LDL- C-LDL cholesterol.

Table 4.61: Effects of oral administration of aqueous extracts of *M. subcordata* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight on biochemical markers of liver and pancreas function

Treatment	Enzyme activity					
	ALT (U/L)	AST (U/L)	ALP (U/L)	γ-GT (U/L)	LDH (U/L)	α-AMY (U/L)
Maerua subcordata (mg/kg body weight)						
Control	26.48±5.9^{A}	238.1±49.8^{A}	11.8±4.5^{A}	7.8±4.2^{A}	1483.0±570.5^{A}	741.2±306.8^{A}
450	72.2±29.4^{A}	279.8±153.6^{A}	13.9±14.0^{A}	5.5±9.2^{A}	2152.6±593.2^{A}	1525.4±217.2^{B}
670	46.4±19.9^{A}	195.5±66.2^{A}	10.7±9.6^{A}	5.2±3.6^{A}	1632.4±196.9^{A}	1302.4±219.8^{B}
1000	74.9±69.5^{A}	313.0±93.9^{A}	37.2±27.6^{A}	2.0±1.0^{A}	1491.4±336.9^{A}	1182.8±287.8^{AB}

Values expressed as Mean ± SD. Means within respective columns followed by similar upper case letters are not significantly different at $p \leq 0.05$. ALT-Alanine aminotransferase, AST- Aspartate aminotransferase, ALP-Alkaline phosphatase, γ GT- gamma glutamyltransferase, LDH- Lactate dehydrogenase and α AMY- alpha Amylase.

Intraperitoneal administration of aqueous extracts of *M. subcordata* to mice daily for 28 days at the three tested doses resulted in a non-significant effect on the levels of UREA, UA, T-CHOL, TG, HDL-C, LDL-C, ALT, AST, ALP, and LDH which were comparable to that of the normal control mice group ($\rho > 0.05$). Extract-treated mice group at 1000 mg/kg body weight caused a significant decrease in the level of CREAT compared to that of the normal control mice group ($\rho < 0.05$). Extract-treated mice groups at 450 and 670 mg/kg body weight caused similar effects to the level of UREA which were comparable to that of the normal control mice group ($\rho > 0.05$). Extract-treated mice groups at 450, 670 and 1000 mg/kg body weight caused similar effects to the levels of CREAT ($\rho > 0.05$).

Extract-treated mice groups at 450 mg/kg body weight caused a significant increase to the level of T-BIL and D-BIL compared to that of the normal control mice group ($\rho < 0.05$). Extract-treated mice groups at 670 and 1000 mg/kg body weight caused similar levels of T-BIL and D-BIL which were comparable to that of the normal control mice group ($\rho > 0.05$). Extract-treated mice groups at 450, 670 and 1000 mg/kg body weight caused similar effects to the level of T-BIL and D-BIL ($\rho > 0.05$).

Extract-treated mice groups at 450 and 670 mg/kg body weight caused similar effects to the level of γ-GT which were significantly higher than that of the normal control mice group. Extract-treated mice groups at 1000 mg/kg body weight caused a non-significant effect to the level of γ-GT relative to that of the normal control mice group ($\rho > 0.05$). Extract-treated mice groups at 450, 670 and 1000 mg/kg body weight caused similar

effects to the level of γ-GT ($\rho > 0.05$). Extract-treated mice groups at 450, 670 and 1000 mg/kg body weight caused similar effects to the level of α-AMY ($\rho > 0.05$) which were significantly higher than that of the normal control mice group ($\rho < 0.05$) (Table 4.62; Table 4.63).

Table 4.62: Effects of intraperitoneal administration of aqueous extracts of *M. subcordata* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight on biochemical markers of kidney and liver function

	Biochemical parameters								
Treatment	UREA (mmol/L)	CREAT (µmol/L)	T-BIL (µmol/L)	D-BIL (µmol/L)	UA (µmol/L)	T-CHOL (mmol/L)	TG (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)
Maerua subcordata (mg/kg body weight)									
Control	8.1±3.0^{A}	43.3±6.7^{A}	8.8±3.6^{A}	0.6±0.9^{A}	5.4±0.6^{A}	4.7±1.5^{A}	1.1±0.5^{A}	0.3±0.1^{A}	0.1±0.0^{A}
450	14.0±9.3^{A}	37.8±2.4^{AB}	24.2±15.6^{B}	10.0±6.4^{B}	5.5±0.4^{A}	2.1±0.7^{A}	1.0±0.2^{A}	0.4±0.2^{A}	0.4±0.1^{A}
670	9.0±2.9^{A}	19.2±3.3^{AB}	13.9±2.2^{AB}	4.8±1.9^{AB}	5.7±0.3^{A}	2.5±0.9^{A}	1.1±0.6^{A}	0.4±0.1^{A}	0.4±0.1^{A}
1000	6.9±2.5^{A}	34.6±25.1^{B}	12.1±4.5^{AB}	5.0±2.7^{AB}	6.2±0.5^{A}	3.7±1.6^{A}	1.0±0.6^{A}	0.5±0.3^{A}	0.4±0.1^{A}

Values expressed as Mean ± SD. Means within respective columns followed by similar upper case letters are not significantly different at $p \leq 0.05$. CREAT = Creatinine, T-BIL = Total bilirubin, D-BIL = Direct bilirubin, UA = Uric acid, CHOL = Cholesterol, TG = Triacylglycerols, HDL-C = HDL Cholesterol and LDL-C = LDL cholesterol.

Table 4.63: Effects of intraperitoneal administration of aqueous extracts of *M. subcordata* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight on biochemical markers of liver and pancreas function

Treatment	**Enzyme activity**					
	ALT (U/L)	AST (U/L)	ALP (U/L)	γ-GT (U/L)	LDH (U/L)	α-AMY (U/L)
Maerua subcordata (mg/kg body weight)						
Control	0.8±0.8^{A}	21.7±13.1^{A}	197.7±65.4^{A}	4.7±1.5^{B}	68.2±21.6^{A}	1315.2±686.2^{A}
450	10.2±6.4^{A}	49.6±16.3^{A}	217.9±26.6^{A}	2.1±0.7^{A}	386.7±154.2^{A}	1535.0±478.5^{B}
670	5.0±1.8^{A}	71.8±49.4^{A}	264.2±115.0^{A}	2.5±0.9^{A}	386.1±321.5^{A}	1108.2±393.5^{B}
1000	5.1±2.8^{A}	114.1±73.9^{A}	205.4±148.8^{A}	3.7±1.6^{AB}	334.4±88.6^{A}	1760.2±427.2^{B}

Values expressed as Mean ± SD. Means within respective columns followed by similar upper case letters are not significantly different at $p \leq 0.05$. ALT-Alanine aminotransferase, AST-Aspartate aminotransferase, ALP-Alkaline phosphatase, γ GT-gamma glutamyltransferase, LDH- Lactate dehydrogenase and α AMY- alpha Amylase.

The effects of oral and intraperitoneal administration of aqueous extracts of *P. capensis* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight on some blood analytes is shown in Table 4.64 to Table 4.67. Results show that oral administration of aqueous extracts of *P. capensis* to mice daily for 28 days at the three tested doses caused similar effects to the levels of UREA, CREAT, T-BIL, D-BIL, TG, HDL-C, LDL-C, ALT, ALP, GGT and LDH which are comparable to that of the normal control mice group. Extract-treated mice groups at 450 and 1000 mg/kg body weight caused similar effects to the level of UA which were comparable to that of the normal control mice group ($\rho > 0.05$). Extract-treated mice groups at 670 and 1000 mg/kg body weight caused similar effects to the level of UA which were comparable to that of the normal control mice group ($\rho > 0.05$). Extract-treated mice group at 450 mg/kg body weight caused a significantly lower level of UA compared to that of the extract-treated mice group at 670 mg/kg body weight ($\rho < 0.05$).

Extract-treated mice group at 450 mg/kg body weight caused a significant increase in T-CHOL compared to that of the normal control mice group ($\rho < 0.05$). Extract-treated mice groups at 670 and 1000 mg/kg body weight caused similar effects to the level of T-CHOL which were comparable to that of the normal control mice group ($\rho > 0.05$). Extract-treated mice group at 450 mg/kg body weight caused a significantly higher level of T-CHOL compared to extract-treated mice group at 1000 mg/kg body weight ($\rho < 0.05$).

Extract-treated mice groups at 450 and 1000 mg/kg body weight caused similar effects to the level of AST which were comparable to that of the normal control mice group ($\rho > 0.05$). Extract-treated mice groups at 670 and 1000 mg/kg body weight caused similar effects to the level of AST which were comparable to that of the normal control mice group ($\rho > 0.05$). Extract-treated mice group at 450 mg/kg body weight caused a significantly lower level of AST compared to that of the extract-treated mice group at 670 mg/kg body weight ($\rho < 0.05$).

Extract-treated mice groups at 450 mg/kg body weight caused a significant increase in the level of α-AMY compared to that of the normal control mice group ($\rho < 0.05$). Extract-treated mice group at 670 and 1000 mg/kg body weight caused similar effects to the level of α-AMY which were comparable to that of the normal control mice group ($\rho > 0.05$). Extract-treated mice group at 450 mg/kg body weight caused a significant increase in the level of α-AMY compared to the extract-treated mice group at 1000 mg/kg body weight ($\rho < 0.05$) (Table 4.64; Table 4.65).

Table 4.64: Effects of oral administration of aqueous extracts of *P. capensis* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight on biochemical markers of kidney and liver function

	Biochemical parameters								
Treatment	UREA (mmol/L)	CREAT (µmol/L)	T-BIL (µmol/L)	D-BIL (µmol/L)	UA (µmol/L)	T-CHOL (mmol/L)	TG (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)
Pappea capensis (mg/kg body weight)									
Control	5.4±1.6^{A}	55.1±12.6^{A}	12.9±9.1^{A}	0.4±0.4^{A}	12.4±4.3^{AB}	0.9±0.5^{A}	1.3±1.1^{A}	0.3±0.1^{A}	0.6±0.2^{A}
450	6.2±2.3^{A}	44.9±6.9^{A}	14.5±7.1^{A}	0.9±0.7^{A}	8.3±2.0^{A}	1.9±0.7^{B}	0.3±0.1^{A}	0.7±0.4^{A}	0.7±0.2^{A}
670	5.7±1.5^{A}	49.4±9.6^{A}	12.6±6.1^{A}	0.6±0.4^{A}	16.0±4.8^{B}	1.2±0.3^{AB}	0.3±0.1^{A}	0.6±0.4^{A}	0.6±0.2^{A}
1000	3.9±0.6^{A}	43.6±10.0^{A}	5.9±3.1^{A}	0.3±0.1^{A}	10.6±3.6^{AB}	0.9±0.3^{A}	0.6±0.5^{A}	0.3±0.1^{A}	0.6±0.2^{A}

Values expressed as Mean ± SD. Means within respective columns followed by similar upper case letters are not significantly different at $p \leq 0.05$. CREAT- Creatinine, T-BIL- Total bilirubin, D-BIL- Direct bilirubin, UA- Uric acid, CHOL- Cholesterol, TG- Triglycerides, HDL-C –HDL Cholesterol and LDL- C-LDL cholesterol.

Table 4.65: Effects of oral administration of aqueous extracts of *P. capensis* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight on biochemical markers of liver and pancreas function

Treatment	**Enzyme activity**					
	ALT (U/L)	AST (U/L)	ALP (U/L)	γ-GT (U/L)	LDH (U/L)	α-AMY (U/L)
Pappea capensis(mg/kg body weight)						
Control	26.5±5.9^{A}	238.1±49.8^{AB}	11.8±4.5^{A}	7.8±4.2^{A}	1483.0±570.5^{A}	741.2±306.8^{A}
450	28.6±20.0^{A}	189.2±75.3^{A}	6.8±5.0^{A}	6.6±3.1^{A}	1839.8±219.8^{A}	1401.4±193.8^{B}
670	72.4±32.4^{AB}	307.0±73.4^{B}	20.6±8.3^{A}	4.5±2.2^{A}	1954.6±580.7^{A}	1052.2±89.2^{AB}
1000	30.8±21.9^{A}	231.6±28.1^{AB}	13.9±12.1^{A}	9.9±12.8^{A}	1685.8±167.0^{A}	999.4±157.7^{A}

Values expressed as Mean ± SD. Means within respective columns followed by similar upper case letters are not significantly different at $p \leq 0.05$. ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, ALP = Alkaline phosphatase, γ-GT = gamma glutamyltransferase, LDH = Lactate dehydrogenase and α-AMY = alpha Amylase.

Intraperitoneal administration of aqueous extracts of *P. capensis* to mice daily for 28 days at the three tested doses resulted in a non-significant effect to the levels of CREAT, T-BIL, UA, T-CHOL, TG, HDL-C, ALT, AST, ALP, LDH and α-AMY which were comparable to that of the normal control mice group ($\rho > 0.05$). Extract-treated mice groups at 450 mg/kg body weight caused a non-significant effect to the level of UREA ($\rho > 0.05$) compared to that of the normal control mice group which was significantly higher ($\rho < 0.05$) than those of the extract-treated mice groups at 670 and 1000 mg/kg body weight; extract-treated mice groups at 670 and 1000 mg/kg body weight caused similar effects to the level of CREAT ($\rho > 0.05$). Extract-treated mice groups 450, 670 and 1000 mg/kg body weight caused similar effects to the level of D-BIL ($\rho > 0.05$) which were significantly higher than that of the normal control mice group ($\rho < 0.05$). Extract-treated mice group at 450 mg/kg body weight and the normal control mice group caused similar effects to the level LDL-C ($\rho < 0.05$) which were significantly lower than those of extract-treated mice groups at 670 and 1000 mg/kg body weight ($\rho < 0.05$); extract-treated mice groups at 670 and 1000 mg/kg body weight caused similar effects to the level of LDL-C ($\rho > 0.05$) (Table 4.66; Table 4.67).

Table 4.66: Effects of intraperitoneal administration of aqueous extracts of *P. capensis* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight on biochemical markers of kidney and liver function

	Biochemical parameters								
Treatment	**UREA (mmol/L)**	**CREAT (µmol/L)**	**T-BIL (µmol/L)**	**D-BIL (µmol/L)**	**UA (µmol/L)**	**TCHOL (mmol/L)**	**TG (mmol/L)**	**HDL-C (mmol/L)**	**LDL-C (mmol/L)**
Pappea capensis (mg/kg body weight)									
Control	8.1±3.0^{B}	43.3±6.7^{A}	8.8±3.6^{A}	0.6±0.9^{B}	5.4±0.6^{A}	4.7±1.5^{A}	1.1±0.5^{A}	0.3±0.1^{A}	0.1±0.1^{A}
450	7.1±0.5^{B}	46.6±7.9^{A}	24.2±15.1^{A}	10.3±6.4^{A}	5.6±0.8^{A}	8.1±2.3^{A}	1.0±0.3^{A}	0.4±0.1^{A}	0.0±0.0^{A}
670	0.6±0.3^{A}	46.2±6.2^{A}	13.9±2.2^{A}	5.0±1.8^{A}	5.4±0.7^{A}	6.0±2.8^{A}	1.0±0.3^{A}	0.8±0.6^{A}	0.4±0.2^{B}
1000	0.4±0.3^{A}	51.4±9.3^{A}	12.1±4.5^{A}	5.1±2.8^{A}	6.2±0.4^{A}	7.4±2.4^{A}	0.9±0.2^{A}	0.5±0.1^{A}	0.6±0.2^{B}

Values expressed as Mean ± SD. Means within respective columns followed by similar upper case letters are not significantly different at $p \leq 0.05$. CREAT- Creatinine, T-BIL- Total bilirubin, D-BIL- Direct bilirubin, UA- Uric acid, CHOL- Cholesterol, TG- Triglycerides, HDL-C –HDL Cholesterol and LDL- C-LDL cholesterol.

Table 4.67: Effects of intraperitoneal administration of aqueous extracts of *P. capensis* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight on biochemical markers of liver and pancreas function

	Enzyme activity					
Treatment	**ALT(U/L)**	**AST(U/L)**	**ALP (U/L)**	**γ GT (U/L)**	**LDH (U/L)**	**α AMY (U/L)**
Pappea capensis (mg/kg body weight)						
Control	0.8±0.4^{A}	197.7±65.4^{A}	21.7±13.1^{A}	6.1±2.7^{A}	68.2±21.6^{A}	1315.2±686.2^{A}
450	0.3±0.1^{A}	178.3±28.3^{A}	32.4±9.9^{A}	8.1±2.3^{B}	106.9±29.7^{A}	1796.6±592.4^{A}
670	0.4±0.2^{A}	222.4±41.9^{A}	19.3±9.6^{A}	6.0±2.8^{AB}	89.4±44.4^{A}	1170.4±739.3^{A}
1000	0.6±0.3^{A}	245.1±8.8^{A}	23.6±7.2^{A}	7.4±2.4^{B}	104.0±18.7^{A}	2024.0±564.9^{A}

Values expressed as Mean ± SD. Means within respective columns followed by similar upper case letters are not significantly different at $p \leq 0.05$. ALT-Alanine aminotransferase, AST- Aspartate aminotransferase, ALP- Alkaline phosphatase, γ GT- gamma glutamyltransferase, LDH- Lactate dehydrogenase and α AMY- alpha Amylase.

4.8 Histopathological studies

Oral and intraperitoneal administration of aqueous extracts of the five medicinal plants to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight caused no observable histopathological changes in the brain, heart, and testes. However, oral and intraperitoneal administration of aqueous extracts of *C. dependens*, *P. capensis*, *S. cordutum* and *M. subcordata* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight caused histological changes in the liver, kidney, lungs and spleen; the effects of some of these extracts to the histopathology of the organ studied varied according to the extract dose administered compared to that of the normal control mice group (Plate 2-6). Oral administration of aqueous extracts of *C. dependens* to mice daily for 28 days at 450, 670 and 1000 mg/kg body weight had no significant histological changes on the liver, kidney, lungs and spleen. Intraperitoneal administration of aqueous extracts of *C. dependens* to mice daily for 28 days at 450 and 670 mg/kg body weight had significant effects on the liver and lungs compared to that of the normal control mice group (Plate 8-14). The liver showed focal foci and periportal accumulation of inflammatory cells whereas the lungs showed extensive infiltration of inflammatory cells around the blood vessels and bronchi with hypertrophy of the bronchi which is indicative of cellular damage. At 1000 mg/kg body weight, the same extract administered intraperitoneally had no significant histopathological effects at cellular levels on the liver, kidney, heart, lungs, spleen and testes relative to that of the normal control mice group.

Oral administration of aqueous extracts of *P. capensis* to mice daily for 28 days at 450 and 670 mg/kg body weight showed no significant histopathological effects at cellular level on the liver, kidney, heart, lungs, spleen and testes compared to those of the normal control mice group. However, oral administration of the same aqueous extract at 1000 mg/kg body weight had significant histopathological changes on the liver compared to that of the normal control mice group. There was the presence of deep staining cell nucleus in the kupffer cells of the liver which is indicative of degenerative features (Plate 6).

Intraperitoneal administration of aqueous extracts of *C. dependens* to mice daily for 28 days at the three doses had significant histopathological effects on the liver, kidney and spleen compared to that of the normal control mice group. The liver demonstrated widespread periportal accumulation of lymphocytic inflammatory cells and picnotic hepatocytes (Plate 8). The kidneys showed an impression of glomerulonephritis (Plate 4 and 5) due to presence of prominent mesenchymal cells, loss of bowmans space and accumulation of inflammatory cells (Plate 2 and 3) whereas the spleen showed extensive lymphocytic infiltration with fibrosis (Plate 17).

Oral administration of aqueous extracts of *S. cordutum* to mice daily for 28 days at the three tested doses had no significant histopathological effects on the liver, kidney, heart, lungs, spleen and testes relative to that of the normal control mice group whereas intraperitoneal administration of aqueous extracts of the same plant to mice daily for 28 days at the three tested doses triggered mild accumulation of inflammatory cells in the

hepatocytes compared to that of the normal control mice group. This may be indicative of early degenerative changes in the hepatocytes.

Oral and intraperitoneal administration of aqueous extracts of *M. subcordata* to mice daily for 28 days at 450 and 670 mg/kg body weight caused no significant histopathological effects on the liver, kidney, heart, lungs, spleen and testes compared to that of the normal control mice group. However at high dose of 1000 mg/kg body weight oral and intraperitoneal administration of the same plant extract at the three tested doses caused significant histopathological effects on the liver compared to that of the normal control mice group. Periportal and other focal foci of inflammatory cell infiltration is a feature of degenerative changes in the hepatocytes. Oral and intraperitoneal administration of stem bark aqueous extracts of *M. undata* to mice daily for 28 days at the three tested doses caused significant histopathological changes at cellular level of the liver, lungs and spleen in comparison to that of the normal control mice group (Plate 16). The most affected organ was the lungs where there was mild to extensive pneumonia and lung edema in a dose independent manner. There was evidence of degenerative cellular changes in the liver with focal accumulation of inflammatory cells. The spleen showed extensive lymphocytic infiltration with fibrosis. There were no much histopathological effects of this plant extract on the kidney, the brain and testis.

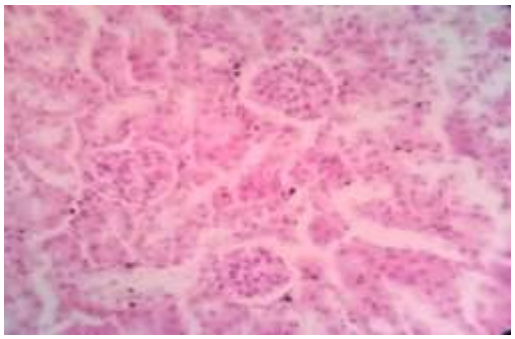

Plate 1: Normal kidney from a mouse orally treated with 0.1ml normal saline. Magnification x 400.

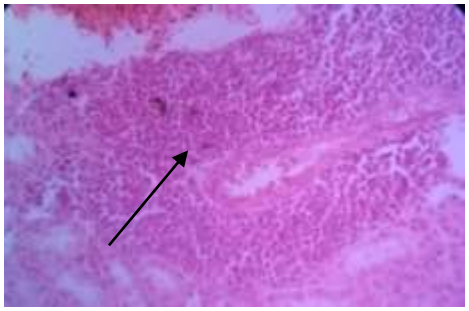

Plate 2: Kidney tissue from mouse intraperitoneally administered with aqueous extracts of *P. capensis* at dose of 1000 mg/kg body weight showing infiltration of mononuclear cells (interstitial nephritis). Magnification x400.

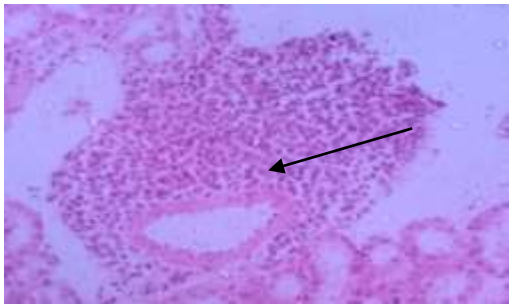

Plate 3: Kidney tissue from mouse intraperitoneally administered with 670 mg/kg body weight of *P. capensis* showing mild interstitial nephritis. Magnification x400.

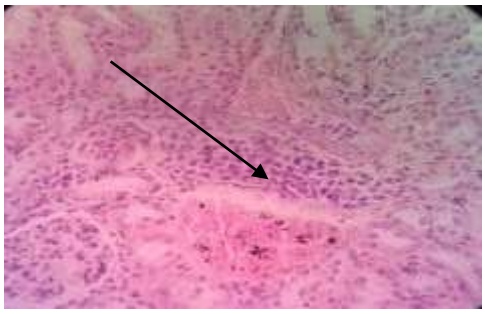

Plate 4: Kidney tissue from mouse orally administered with aqueous extracts of *P. capensis* at dose of 450 mg/kg body weight showing peritubular accumulation of inflammatory cells. Magnification x400.

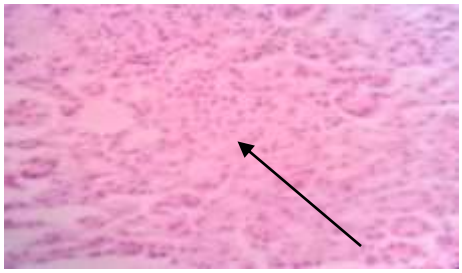

Plate 5: Kidney tissue from mouse orally treated with extracts of *P. capensis* at a dose of 1000 mg/kg body weight showing few cells in the glomeruli and No bowman's space. Magnification x400.

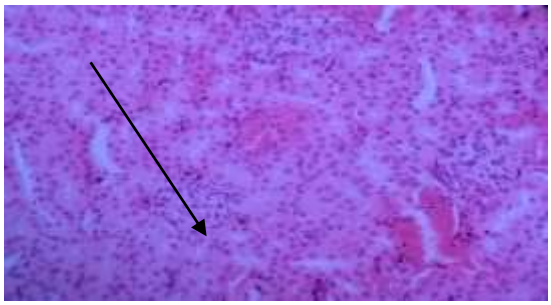

Plate 6: Kidney tissue from mouse treated with *P. capensis* extract at 450 mg/kg body weight showing deep staining picnotic cells. Magnification x400.

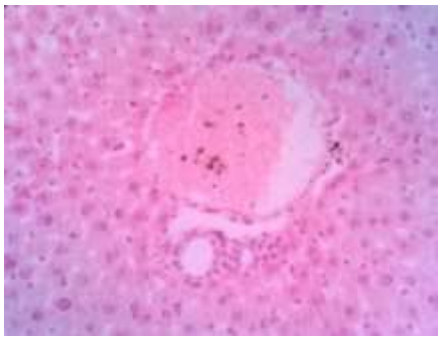

Plate 7: Normal liver tissue section from mouse intraperitoneally administered with 0.1ml normal saline. Magnification x 400.

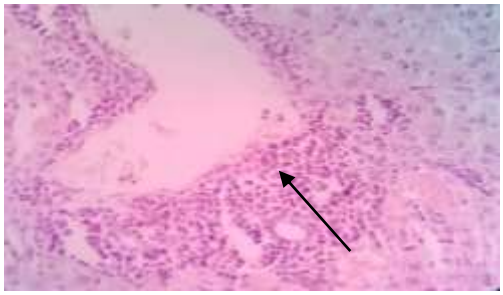

Plate 8: Liver tissue section from mouse intraperitoneally administered with 450 mg/kg body weight of aqueous extracts of *P. capensis* showing periportal accumulation of inflammatory cells in the liver. Magnification x 400.

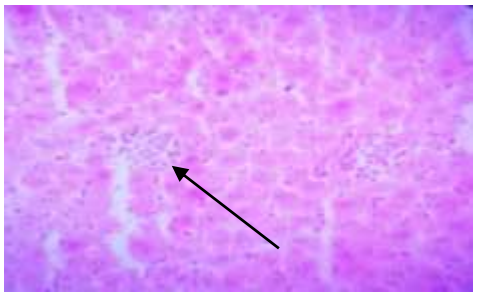

Plate 9: Liver tissue section from mouse intraperitoneally administered with 670 mg/kg body weight of aqueous extracts of *C. dependens* showing focal foci of inflammatory cells. Magnification x 400.

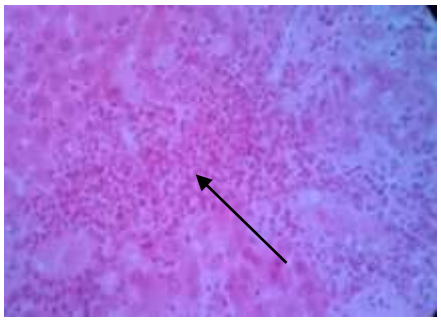

Plate 10: Liver tissue section from mouse intraperitoneally administered with 1000 mg/kg body weight of aqueous extracts of *C. dependens* showing edematous areas and focal accumulation of inflammatory cells. Magnification x400.

Plate 11: Normal lung tissue section from a mouse intraperitoneally administered with 0.1ml physiological saline. Magnification x 400.

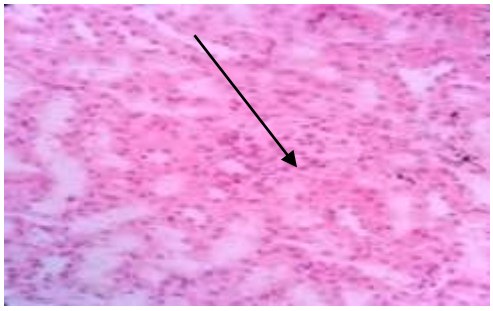

Plate 12: Lung tissue section from mouse intraperitoneally administered with 670 mg/kg body weight of aqueous extracts of *C. dependens* showing infiltration of inflammatory cells. Magnification x400.

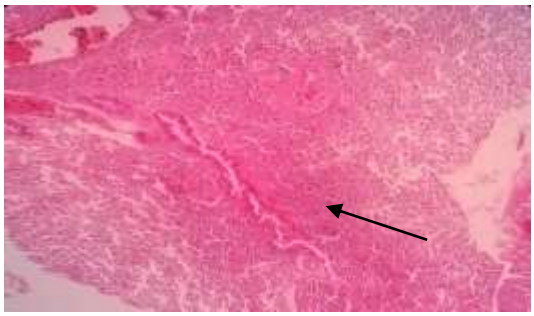

Plate 13: Lung tissue section from mouse intraperitoneally administered with 1000 mg/kg body weight of aqueous extracts of *M. undata* showing features of severe pneumonitis. Magnification x400.

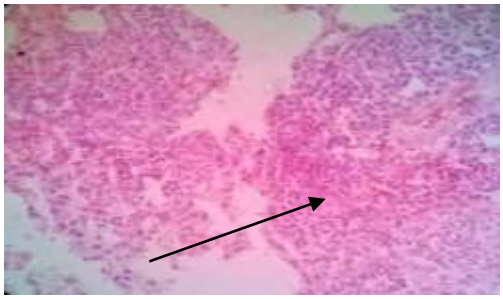

Plate 14: Lung tissue section from mouse intraperitoneally administered with 1000 mg/kg body weight of aqueous extracts of *M. undata* showing features of severe pneumonitis. Magnification x400.

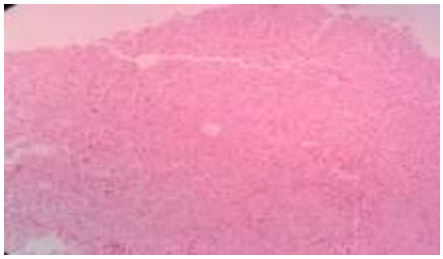

Plate 15: Normal spleen from mouse orally treated with 0.1ml physiological saline. Magnification x400.

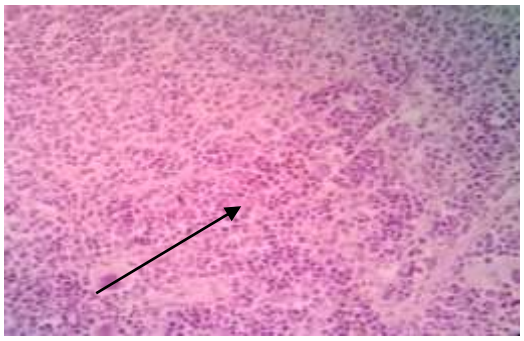

Plate 16: Spleen tissue section from mouse intraperitoneally administered with 1000 mg/kg body weight of aqueous extracts of *M. undata* showing extensive lymphocytic infiltration with fibrosis. Magnification x400.

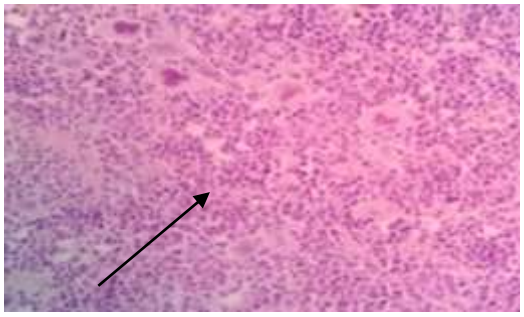

Plate 17: Spleen tissue section from mouse intraperitoneally administered with 670 mg/kg body weight of aqueous extracts of *P. capensis* showing features of extensive lymphocytic infiltration with fibrosis. Magnification x400.

4.9 Quantitative analysis of the phytochemical composition of aqueous extracts of the five studied medicinal plants

Five phytochemicals were quantitatively estimated in the five aqueous medicinal plants extracts studied (Table 4.68). *Mayrtenus undata* had the highest concentration of Tannins and saponins while *Maerua subcordata* had the lowest. The highest content of total phenols was found in *Maerua subcordata* while high content of flavonoids and alkaloids was found in *Pappea capensis*.

Table 4.68: Phytochemical composition of the five aqueous plants extracts

Samples	**Phytochemical Content (mg/g)**				
	Tannins	**Total Phenols**	**Flavonoid**	**Saponin**	**Alkaloids**
Chasmanthera dependens	1.0±0.1	0.5±0.0	14.6±0.6	67.1±2.4	79.0±1.5
Mayrtenus undata	2.3±0.1	0.5±0.0	150.8±6.7	109.5±9.1	106.4±3.9
Syzigium cordatum	1.9±0.1	0.4±0.0	55.9±4.7	60.5±0.9	74.9±5.3
Maerua subcordata	0.3±0.0	0.8±0.1	22.5±0.6	92.5±0.4	94.4±2.9
Pappea capensis	2.1±0.1	0.5±0.1	179.0±6.2	41.7±3.7	136.7±1.1

4.10 Trace element composition of the five aqueous plants and the amounts administered to each mouse

The trace element composition of the five aqueous plants extracts studied are as shown in Table 4.69. Results show that all the plant extracts contained K^{+}, Ca^{2+}, Cr^{6+}, V^{3+}, Mn^{2+}, Fe^{2+}, Cu^{2+}, Zn^{2+}, Se^{2+}, As^{5+}, Hg^{2+} Rb^{2+}, Br^{2+} and $Pb^{+,}$ Ti and Sr at varying levels. Potassium was found to be elevated in *M. subcordata, C. dependens* and *S. cordatum*. *M. undata* had the highest concentration of calcium though within the allowable limit. The amount of trace elements present in the dosages given to mice in toxicity studies was within the required daily allowance except for Manganese in *P. capensis* which was slightly higher (Tables 4.69).

Table 4.69: Mineral elements composition of the five aqueous plants extracts and the amounts administered to each mouse (ppb)

Element	***Maerua subcordata***	***Chasmanthera dependens***	***Mayrtenus undata***	***Pappea capensis***	***Syzigium cordatum***	**RDA for mice (µg/day)**
K	727853 ± 13552	7871865 ± 245645	347780 ± 3854	1168740 ± 15080	519492 ± 13550	$3.5x10^6$ **(1250)**
450mg	7.5	81.5	3.6	12.1	5.4	
670mg	11.2	121.3	5.4	18.1	8.0	
1000mg	16.7	181.1	8.0	26.9	12.0	
Ca	736483 ± 9265	614592 ± 19765	823688 ± 8394	178467 ± 2531	378770 ± 13911	$1.0x10^6$ **(357.1)**
450mg	7.6	6.4	8.5	1.9	3.9	
670mg	11.4	9.5	12.7	2.8	5.8	
1000mg	16.9	14.1	19.0	4.1	8.7	
Ti	<280	<280	2628 ± 90	527 ± 42	4043 ± 180	
450mg	0.0	0.0	0.0	0.0	0.0	
670mg	0.0	0.0	0.0	0.0	0.1	
1000mg	0.0	0.0	0.1	0.0	0.1	
V	<230	655 ± 52	1258 ± 63	1043 ± 68	1269 ± 107	$<1.8x10^3$ **(0.64)**
450mg	0.0	0.0	0.0	0.0	0.0	
670mg	0.0	0.0	0.0	0.0	0.0	
1000mg	0.0	0.0	0.0	0.0	0.0	
Cr	<150	<150	<150	700 ± 49	<150	3.5 x 10 **(12.5)**
450mg	0.0	0.0	0.0	0.0	0.0	
670mg	0.0	0.0	0.0	0.0	0.0	
1000mg	0.0	0.0	0.0	0.0	0.0	
Mn	1714 ± 56	3809 ± 173	588 ± 36	144350 ± 1901	16128 ± 353	$2.3 x10^3$ **(0.82)**
450mg	0.0	0.0	0.0	**1.5**	0.2	
670mg	0.0	0.1	0.0	**2.2**	0.3	
1000mg	0.0	0.1	0.0	**3.3**	0.4	
Fe	5350 ± 101	5098 ± 208	6737 ±102	5978 ± 111	25676 ± 504	$8.0 x 10^3$

450mg	0.0	0.1	0.1	0.1	0.3	**(2.9)**
670mg	0.0	0.1	0.1	0.1	0.4	
1000mg	0.0	0.1	0.2	0.1	0.6	
Cu	322 ± 20	685 ± 43	242 ± 17	272 ± 18	239 ± 27	1.5×10^3
450mg	0.0	0.0	0.0	0.0	0.0	**(0.54)**
670mg	0.1	0.0	0.0	0.0	0.0	
1000mg	0.1	0.0	0.0	0.0	0.0	
Zn	3562 ± 64	3968 ± 151	1030 ± 25	1469 ± 34	1267 ± 45	1.1×10^4
450mg	0.0	0.0	0.0	0.0	0.0	**(3.9)**
670mg	0.0	0.1	0.0	0.0	0.0	
1000mg	0.0	0.1	0.0	0.0	0.0	
As	171 ± 12	176 ± 15	57.7 ± 9.7	74.0 ± 1.2	127 ± 11	
450mg	0.0	0.0	0.0	0.0	0.0	
670mg	0.0	0.0	0.0	0.0	0.0	
1000mg	0.0	0.0	0.0	0.0	0.0	
Se	<40	<40	<40	<40	<40	3.5x10
450mg	0.3	0.0	0.0	0.0	0.0	**(0.0125)**
670mg	0.4	0.0	0.0	0.0	0.0	
1000mg	0.6	0.0	0.0	0.0	0.0	
Br	27156 ± 354	4864 ± 174	1065 ± 22	9880 ± 143	6691 ± 136	
450mg	0.0	0.1	0.0	0.1	0.1	
670mg	0.0	0.1	0.0	0.2	0.1	
1000mg	0.0	0.1	0.0	0.2	0.2	
Rb		1857 ± 76	319 ± 14	3532 ± 59	425 ± 25	
450mg		0.0	0.0	0.0	0.0	
670mg		0.0	0.0	0.1	0.0	
1000mg		0.0	0.0	0.1	0.0	
Sr	3008 ± 153	6608 ± 233	14303 ± 162	1193 ± 29	2305 ± 62	
450mg	0.3	0.1	0.2	0.0	0.0	
670mg	0.4	0.1	0.2	0.0	0.0	
1000mg	0.6	0.2	0.3	0.0	0.1	

Hg	<100	<100	<100	<100	<100	
450mg	0.0	0.0	0.0	0.0	0.0	
670mg/kgbwt	0.0	0.0	0.0	0.0	0.0	
1000mg/kgbwt	0.0	0.0	0.0	0.0	0.0	
Pb	218 ± 18	341 ± 29	77.0 ± 1.3	<80	212 ± 17	
450mg	0.0	0.0	0.0	0.0	0.0	
670mg	0.0	0.0	0.0	0.0	0.0	
1000mg	0.0	0.0	0.0	0.0	0.0	

Concentration of each mineral are expressed as µg/kg of dry powder of the five studied plants and are in the upper row of each plant; the amount of each mineral administered to mice in µg based on its concentration in each plant extract is in the lower rows. This is compared with the recommended daily allowance shown in the last column and RDA in mice (in brackets). Recommended daily allowance is estimated from that of human beings stated in Strain and Cashman (2009).

CHAPTER FIVE

DISCUSSION, CONCLUSIONS AND RECOMMENDATIONS

5.1 DISCUSSION

The alloxan induced diabetic mouse model that was used in the research had up to five fold increase in blood glucose upon induction (5.1-26.2 mmol/L) relative to that of the control normal mice (Table 4.1 to 4.5). Previous studies show that diabetogenic agents like alloxan monohydrate, given intraperitoneally, induce diabetes type 1 by causing selective necrosis of pancreatic beta-cells of Langerhans resulting in diabetes (Federiuk *et al.,* 2004). The induction of diabetes was done 72 hours before the start of the experiment using alloxan monohydrate at a dose of 186.9 mg/kg body weight (Karau, 2013). Thereafter, different groups of animals were subjected to the four sets of treatment (control normal control mice, diabetic control mice, control diabetic control mice treated with the reference drug and diabetic mice treated with five doses of the five aqueous plant extracts).

Oral and intraperitoneal administration of aqueous extracts of *C. dependens, M. undata*, and *S. cordutum* to alloxan induced diabetic mice at all the five tested doses significantly reduced blood glucose within the study period of twenty-four hours with maximum activity at the eighth hour which was comparable to the effects of the reference drug (Glibenclamide or insulin) (Figure 4.1 to 4.10). This may be attributed to the presence of phytochemicals with hypoglycemic effects (Middleton *et al*., 2000). The low hypoglycemic activity at a dose of 25 mg/kg body weight when given orally may

suggest that the phytochemical content in this therapeutic dose was low and may have been degraded or inactivated by digestive enzymes or may have not attained saturable levels (Njeri *et al*., 2017). When given intraperitoneally, the hypoglycemic effects were significant ($\rho \leq 0.05$) within the first two hours (comparable to the reference drug) as opposed to the oral route where effects were gradual and reached maximum at the eighth hour. This could be attributed to active compounds reaching the systemic circulation faster (Mukundi *et al*., 2015; Abdirahman *et al*., 2015) and the fast pass metabolism realized in the intraperitoneal route (Njogu *et al*., 2016).

However, *M. subcordata* and *P. capensis* extracts when orally and intraperitoneally administered resulted in minimal hypoglycemic activity which was statistically different ($\rho > 0.05$) from those of the diabetic control animals (Figure 4.7 to 4.10). This suggests that the two plants extract contained phytoconstituents which were not readily available or that the phytochemical components in the therapeutic doses used were low. This is in agreement with previous studies on these medicinal plants (Karau, 2014; Arika *et al*., 2016). Oral administration of aqueous extracts of *M. subcordata* to alloxan induced diabetic mice at a dose of 93.5 mg/kg body weight had no hypoglycemic effect. This could be attributed to inhibitory effects in the gastrointestinal tract of glucagon-like peptide-1 (GLP-1) as well as glucose-dependent insulinotropic polypeptide (GIP, previously called gastric inhibitory peptide) which suppressed insulin production (Maria *et al*., 2015). It could also have been as a result of the levels of astringent tannins in this dose which provoked regurgitation by the mice (Kumar *et al*., 2012). The hypoglycemic effect in all the five extracts was in a dose independent manner suggesting that the

minimum dose was sufficient enough to effect maximum hypoglycemic activity. It could also suggest that the aqueous plants extracts exerted their effects in a saturable manner and this was in agreement with previous studies on these aqueous plants extracts (Arika *et al*., 2016).

These results indicate that the most effective plant extract in terms of hypoglycemic activity was *S. cordutum* followed by *C. dependens* and *M. undata* while the least active was *M. subcordata* after *P. capensis.* Extract administration via the intraperitoneal route exhibited better hypoglycemic activity than the administration via the oral route in all the five studied extracts. *S. cordutum* and *C. dependens* contained moderate amounts of phytonutrients and was rich in iron. This is an indication that maximum activity could be achieved with minimum concentrations of phytonutrients. The better antidiabetic effect demonstrated by the plant extracts administered via the intraperitoneal route relative to the oral route could be due to the fact that in the oral route the constituents may have been transported more slowly across the intestinal wall via the portal vein to the liver subjecting it to the first pass metabolism while in the intraperitoneal route the active compounds reached the systemic circulation faster (Arika *et al*., 2014). These results are in agreement with previous studies done on extracts of these medicinal plants (Mukundi *et al.,* 2015; Abdirahman *et al.,* 2015).

The evaluation of average change in body weight over a period of 28 days revealed that indeed there was significant difference ($\rho \leq 0.05$) between the control animals and the high non therapeutic dose treated animals (450, 670 and 1000mg/kg body weight).

There was significant reduction on weekly weight gain which resulted in a reduction in average weekly weight in a dose dependent manner. The dose dependent effects on average weekly body weights was on both the orally and intraperitoneally treated animals where the highest dose of 1000mg/kg body weight gave the greatest loss of weight per week. The weights of the kidney, heart and spleen in relation to total body weight were not significantly different from those of control animals ($\rho > 0.05$) while those of the liver, lungs, brain and testes were statistically different ($\rho \leq 0.05$) from the control animals. This suggests that the extracts contained the phytonutrients that promoted loss of appetite, corroded the intestinal lining or interfered with metabolism as well as enhancing proteolysis in the skeletal muscles resulting into growth retardation (Piero *et al.*, 2015a).

The animals subjected to aqueous extracts of *C. dependens*, *M. undata* and *S. cordutum* had significantly decreased percent brain to body weight and an increased percent liver and lungs to body weight. *C. dependens* significantly increased the weight of the liver in comparison to the control animals. *P. capensis* at a dose of 1000 mg/kg body weight significantly increased the weight of the liver, testis and the heart. These features indicate atrophy and inflammatory effects of the extracts on the organs as reported in histopathological report.

The red blood cell indices are blood tests that provide information about the hemoglobin content and size of red blood cells. Abnormal values indicate the presence and type of anemia. It also gives information on peripheral blood picture and the reticuloendothelial system. The toxicity effects of both oral and intraperitoneal

administration of the aqueous extracts of *M. undata* and *M. subcordata* were significant ($\rho \leq 0.05$) compared to the control animals .There was reduced hemoglobin, red blood cell count, packed cell volume, mean cell volume and increased mean cell hemoglobin concentration on *M. subcordata* extract treated animals suggesting induction of microcytic anemia. However, the animals subjected to aqueous extracts of *M. undata* had reduced Hb, red blood cell count, packed cell volume, mean hemoglobin concentration and an increase in mean cell volume suggesting megaloblastic anemia. The aqueous extracts of *S. cordatum* caused an increase in the platelet count and this indicated thrombocytosis while those subjected to *M. subcordata* had reduced platelets. The rest of the studied plants extracts, *C. dependens* and *P. capensis* had no significant toxic effects on red cell hematological parameters compared to the normal control animals ($\rho > 0.05$). Previous studies on effects of plant extracts on hematological parameters have shown similar findings (Mwale *et al.,* 2013).

The results of this study indicated slight alteration in the white blood cell series for some plant extracts. Other than aqueous extracts of *C. dependens* and *M. subcordata*, the other three plant extracts, *S. cordutum, M. undata* and *P. capensis* reduced total white blood cells and lymphocytes. White blood cell count and its differential count play a vital role in the assessment of the immune function. Neutrophils have phagocytic activities (Dacie and Lewis, 1991) which attack and destroy foreign particles, cell waste materials and bacteria. The lymphocytes help to specifically recognize a diverse range of antigens, differentiate and mature to functional capacity, respond to the antigenic

stimuli and establish immunologic memory (Klein and Horejí, 1997; Patterson *et al.*, 2002).

The results on platelet counts indicated that aqueous stem extracts of *S. cordatum* slightly increased the platelet count while those of *M. subcordata* suppressed thrombopoiesis. Platelets play a very important role in coagulation system and this suggests that the *S. cordatum* extract may be having a stimulatory effect on thrombopoietin (Li, 1999) and therefore, can be used in management of hemophilia. The rest of the plant extracts, *C. dependens, M. undata* and *P. capensis* had no significant effects ($\rho \leq 0.05$) on the platelet counts.

The findings of this study also revealed that most of the biochemical processes were not affected by the aqueous plant extracts under study. Most of the biochemical metabolites analyzed in test animals were comparable to those of normal control animals. Alpha amylase (α-amylase) was unilaterally elevated in all extract treated animals compared to those of normal control animals. This was attributed to the stress that may have been caused by daily dosing as described by Noto *et al.*, (2005). The increase in amylase enzyme activity may have also been caused by pancreatitis resulting from plant extract treatment. The extracts of *M. undata* and *S. cordutum* also showed slight increase in UA, HDL-C and AST activity which may have been triggered by the phytochemicals present in the plant extracts on the liver. The rest of the measured enzymes and metabolites were not significantly altered ($\rho > 0.05$).

Other than *C. dependens* and *P. capensis* extract which slightly raised the T-CHOL and LDL-C, the rest of the studied plant extracts had no significant effects on the lipids when given orally. However, intraperitoneal administration of aqueous extracts of *P. capensis* raised the total cholesterols. In type 2 diabetes, dyslipidemia is characterized through increased levels of serum triacylglycerols (TG) and reduced levels of serum high density lipoproteins (HDL-C), while total cholesterol (T-CHOL) and low density lipoprotein cholesterols (LDL-C) may be either normal or marginally elevated (Buse *et al*., 2004).

The five studied plant extracts contained phytochemicals: alkaloids, saponins, flavonoids, phenols and tannins as well as a wide range of trace elements which in previous studies have demonstrated effects on the activity of pancreatic beta cells, increased inhibitory effect against insulinase enzyme, increased insulin sensitivity or the insulin-like activity of the plant extracts (Ayodhya *et al*., 2010). Other mechanisms may also be involved such as increase of peripheral utilization of glucose, increase in the synthesis of hepatic glycogen or decrease of glycogenolysis, inhibition of intestinal glucose absorption, reduction of glycaemic index of carbohydrates and reduction of the effect of glutathione (Bnouham *et al.*, 2006).

Flavonoids act as natural antioxidants and have an effect on many diseases. They have anti-tumor, anti-inflammatory, anti-allergic, anti-thrombotic, anti-diabetic (Gaur *et al*, .2014) and anti-atherosclerotic activities (Salvamani *et al*., 2014). Flavonoids are the

largest, most varied, and most studied group of phytochemicals and disease risk reducers in epidemiologic studies (Arts *et al*., 2005).

Alkaloids are significant for the protection and survival of plant against micro-organisms (antibacterial and antifungal activities), insects and herbivores and also against other plants by means of allelopathically active chemicals (Molyneux *et a*l., 1996). The use of alkaloids containing plants as dyes, spices, drugs or poisons can be traced back almost to the beginning of civilization. Alkaloids have many pharmacological activities including antihypertensive effects (many indole alkaloids), antiarrhythmic effect (quinidine, spareien), antimalarial activity (quinine), and anticancer actions (dimeric indoles, vincristine, and vinblastine) (Wink *et* al., 1998). Berberine, an isoquinoline alkaloid is obtained from the roots and stem bark of *Berberis* L. (Berberidaceae). Berberine acts as antihyperglycemic agent by inhibiting the activity of disaccharidases in Caco-2 cells. It decreases sucrose activity after pre-incubation with Caco-2 cells for 72 hours. No significant effects on gluconeogenesis and glucose consumption of Caco-2 cells were observed, suggesting that the antihyperglycemic activity of Berberine is due to its ability to inhibit alpha-glucosidase and decrease glucose transport through the intestinal epithelium (Pan *et al*., 2003).

The alkaloid 1-ephedrine promotes the regeneration of pancreas islets following destruction of the beta cells, hence restores the secretion of insulin, and thus corrects hyperglycemia (Piero *et al*., 2015a). Some alkaloids have stimulant property as caffeine and nicotine, morphine are used as the analgesic and quinine as the antimalarial drug.

Alkaloids have been reported to cause liver megalocytosis, proliferation of biliary tract epithelium, liver cirrhosis and nodular hyperplasia (Zeinsteger *et al*., 2003). Some of the toxic alkaloids found in plants include confine, solanine, methyllycaconitine, nudicauline, and geyerline (Gardner and Pfister, 2007), 2-pentylpiperidine (Radulović *et al*., 2011), and pyrrolizidine alkaloids (Wiedenfeld, 2011).

Saponins, their biosynthetic intermediates and derivatives have been ascribed to a number of pharmacological activities, most notably permeabilization of cell membranes, cytotoxic effects on cancerous cells, adjuvant properties, immunomodulatory potential and lowering of serum cholesterol (Sjolander *et al*., 1998; Francis *et al*., 2002; Hostettmann and Marston, 2005; Sun *et al*., 2009; Man *et al*., 2010;).

Tannins reduce feed intake by decreasing palatability and by reducing feed digestion (Piero *et al*., 2015a). Palatability is reduced because tannins are astringent. Astringency is the sensation caused by the formation of complexes between tannins and salivary glycoproteins. Low palatability depresses feed intake. Tannins are divided into two: hydrolysable and condensed tannins. Hydrolysable tannins are converted by microbial metabolism and gastric digestion into absorbable low molecular weight metabolites such as tannic acid which are toxic (Arika *et al*., 2016). The major lesions associated with hydrolysable tannins poisoning are hemorrhagic gastroenteritis which decreases absorption of nutrients, necrosis of the liver, and kidney damage with proximal tubular necrosis (Kumari and Jain, 2012). Protanthocyanidins (PAs) (condensed tannins) retard

growth by inhibiting feed intake and digestibility (Click and Joslyn, 1969). Protanthocyanidins which are not absorbed by the digestive tract, damage the mucosa of the gastrointestinal tract, decreasing the absorption of nutrients such as proteins and carbohydrates and essential amino acids such as methionine and lysine. They also increase excretion of proteins and essential amino acids and alter the excretion of certain cations (Arika *et al*., 2016).

Phenols are known for their anti-hyperglycemic activity (Nkirote *et al*., 2011). Phenols also possess antiviral properties (Lu *et al*., 2004), antibacterial and antiparasitic effect (Akiyama *et al*., 2011). The presence of these phytochemicals correlates with the findings of Baskeran *et al*., (2011).

Phytonutrients are one of the components of food, though they are not synthesized in the body, they are essential for optimal health. Several essential metals are required for the proper functioning of many enzymes, transcriptional factors and proteins important in various biochemical pathways. For example Zn, Mg and Mn are cofactors of hundreds of enzymes, and Zn and Cr are co-factors in the synthesis and secretion of insulin from the pancreatic beta-cells (Gloria *et al*., 2010; Kimura, 1996). Similarly, Cr enhances the insulin receptor activity on target tissues, especially in muscle cells (Abdul *et al*., 2014). Copper (Cu) plays vital role in various metabolic processes. Ceruloplasmin ferroxidase activity and intracellular iron utilization is copper dependent. Superoxide dismutase a powerful antioxidant is a Copper-Zinc dependent enzyme which protects cells against free radical injury just like the Manganese dependent

superoxide dismutase (Tuormaa, 2000). Severe copper deficiency in infants results in pathological bone fractures (cross-links collagen), cardiovascular disorders (cross-links soluble elastin and collagen) and emphysema-like lung condition which are associated with reduced activity of a copper dependent enzyme lysyl oxidase. It can also cause neurological problems such as ataxia, seizures and episodic apnea which could be caused by lack of myelination leading to reduced nerve cell formation during embryonic development (Karau *et al*., 2012).

Iron (Fe) is an essential transition metal required for the synthesis of two important functional proteins such as hemoglobin and myoglobin, which are involved in the transport of molecular oxygen during respiration (Ganz and Nemeth, 2006). It is also required in the elastin production along with Zn and ascorbic acid and collagen synthesis. In blood stream small fraction of serum Fe is transported by glycoprotein transferrin into the cells. In the body tissues, ferritin stores free Fe, which is increased in newly diagnosed diabetic subjects (Kundu *et al*., 2013). Jiang *et al.,* (2003) manifested higher level of ferritin in diabetics as compared to the non-diabetic subjects.

Chromium (Cr) regulates insulin and blood glucose levels by stimulating insulin signaling pathway and metabolism by up-regulating glucose transporter (GLUT4) translocation in muscle cells (Qiao *et al*., 2009). Nickel was found in detectable levels in *A. pluriseta* studies in rats and humans which indicated that Nickel deprivation depresses growth, reproductive performance, and plasma glucose and that it alters the distribution of other elements in the body, including calcium, iron, and zinc (Nielson,

2000). Calcium improves insulin sensitivity in some type 2 diabetic populations (Mukundi *et al.,* 2015). Potassium supplementation yields improved insulin sensitivity, responsiveness and secretion; insulin administration induces a loss of potassium; and a high potassium intake reduces the risk of heart disease, atherosclerosis, and cancer (Norbiato *et al., 1984*).

5.2 CONCLUSIONS

From the study, it can be concluded that;

(i) Other than *P. capensis* and *M. subcordata* which had minimal hypoglycemic activity both in the oral and intraperitoneal routes, the other three plants under study, *C. dependens, M. undata* and *S. cordutum,* had significant hypoglycemic activity when administered both orally and intraperitoneally. The intraperitoneal route exhibited better efficacy than oral route at all doses within the first eight hours.

(ii) Of the five aqueous plant extracts that were given to experimental mice *S. cordutum* was the most effective at lower doses of up to 93.5mg/ kg body weight while *C. dependens* had the highest efficacy at higher doses of 180.9 and 350 mg body weight.

(iii) There were significant losses of weight on the experimental mice orally or intraperitoneally administered with the five plant extracts. The effects on the loss of weights were dose and route dependent where intraperitoneal administration of the high non-therapeutic doses resulted to greater loss of weights compared to the oral administration of the same. Of the five plant

extracts, *S. cordutum* had higher weight losses while *M. subcordata* resulted to lower weight losses. Drastic weight loss was noticed in mice administered with the five aqueous plants extracts at 1000 mg/kg body weight.

(iv) Significant changes in percent organ to body weight in some organs were noticeable. The liver and lungs were enlarged in both oral and intraperitoneal extract treated mice suggesting inflammatory features while the brain reduced in weight indicating atrophy in C. *dependens, S. cordutum* and *M. undata* treated mice.

(v) Oral and intraperitoneal administration of extracts of *M. subcordata* caused microcytic anemia while those of *M. undata* caused macrocytic anemia.

(vi) Oral and intraperitoneal administration of aqueous extracts of C. *dependens, M. undata* and *S. cordatum* altered the levels of lipids.

(vii) Histologically plant extracts of *C. dependence, M. undata* and *P. capensis* triggered accumulation of inflammatory cells especially at high doses of 1000 mg/kg body weight in both the oral and intraperitoneal routes of administration.

(viii) All the five plant extracts contained phytonutrients flavonoids, saponins, tannins, alkaloids and total phenols in moderate amounts. *M. undata* contained the highest concentration of all phytochemicals.

(ix) Elemental analysis of the five aqueous plant extracts revealed the presence of K, Ca, Ti, V, Cr, Mn, Fe, Ni, Cu, Zn, As, Se, Br, Rb, Sr, Hg and Pb minerals. *P. capensis* had the highest concentration of Manganese which was greater than the RDA.

(x) From the study it can be concluded that the plant extracts of *C. dependens, S. cordatum* and *M. undata* had significant hypoglycemic activity and are safe in the management of diabetes mellitus at low doses. The aqueous extract of *M. subcordata* and *P. capensis,* are not significantly hypoglycemic. These then rejects the research hypothesis.

(xi) The hypoglycemic activity of all the extracts revealed that the optimum time of activity was at the eight hour.

5.3 RECOMMENDATIONS

- The plant extracts of *C. dependens, S. cordatum* and *M. undata* were effective in reducing glucose level in diabetic mice. *M. subcordata and P. capensis* showed mild activity. The extracts were most effective through intraperitoneal route but found to be safe when administered orally. The study therefore recommends continued use of the active plant extracts in the management of diabetes mellitus through the oral route at low doses. The hypoglycemic activity and safety demonstrated by the oral and intraperitoneal administration of extracts of *C. dependens, S. cordatum* and *M. undata* to alloxan induced diabetic mice at the tested therapeutic doses could have been caused by the phytochemicals and mineral elements in these plant extracts. Further the presence of toxic phytochemicals and overdose of some mineral elements in these extracts may also be responsible for the observed moderate toxicity in normal control mice used in this study.

5.3.1 RECOMMENDATIONS FOR FURTHER STUDIES

- The individual phytochemical compounds and bioactivity for the active plant species should be established in order to explore possibilities of developing a drug from the plant extracts and promote domestication and conservation of the plants.
- Investigation of combination therapies and toxicity reduction on the active extracts should be done to create a rationale for drug combination in the management of diabetes mellitus using the plant extracts. The effect of the same extracts on higher animals like apes or human beings should be evaluated in order to further confirm their efficacy and safety.
- Innovation of preserveable and consumable products fortified with extracts of these plant species and tablets or capsules should be explored to increase the useful period and avoid toxic fermentation of the aqueous herbal extracts. Effects of organic extracts of the non-active extracts should also be compared to the aqueous extract results.

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APPENDICES

Appendix 1: Diagnostic criteria for DM and two high risk categories of pre-DM (IFG and IGT)

	FPG(mg/dl)	**2-HPG(mg/dl)**	**Sx of diabetes +CPG**
Normal	<100	<140	-
IFG	≥100 & ≤126	-	-
IGT	-	≥140 & >200	-
Diabetes	≥126	≥200	+CPG ≥200mg

FPG- Fasting Plasma Glucose

2-HPG- 2 hour post 75g glucose load plasma glucose

CPG- Casual plasma glucose

Sx- Symptoms of diabetes e.g. polydipsia, polyurea weight loss (Llorente and Malphurs, 2007)

Appendix 2: Preparation of the extracts

For hypoglycemic studies: Dose of25 mg/kg body weight for albino Swiss mice of average weight of 23g, required, 6 mg dissolved in 1 ml of physiological saline. 48.4 mg/kg body weight required 12mg dissolved in 1ml of physiological saline. 93.5 mg/kg body weight required 21.5 mg dissolved in 1 ml of physiological saline. 180.9 mg/kg body weight required 42 mg dissolved in 1 ml of physiological saline. 350 mg/kg body weight required 81 mg of Plant extract dissolved in 1 ml physiological saline.

There were eight groups of animals in the study as follows:

Normal controls to monitor the circadian rhythm (5 animals).

Diabetic controls not on treatment (5 animals).

Diabetic group treated with either insulin or glibenclamide (5 animals).

Diabetic groups treated orally or intraperitoneally:

25mg/kg body weight (5 animals).

48.4mg/kg body weight (5 animals).

93.5mg/kg body weight (5 animals).

180.9mg/kg body weight (5 animals).

350mg/kg body weight (5 animals)

Appendix 3: Percent change in glucose levels after oral and intraperitoneal administration of *C. dependens* at various doses to alloxan induced mice

Treatment	Route	%Glucose levels at different hours after treatment					
		0	2	4	6	8	24
Normal control	Oral	100.0 ± 0.0^{A}	98.6 ± 1.9^{Abc}	99.3 ± 3.1^{Ab}	97.82 ± 2.8^{Ab}	97.9 ± 5.2^{Ab}	99.0 ± 4.6^{Ab}
	IP	100.0 ± 0.0^{A}	101.2 ± 1.6^{Ab}	99.2 ± 1.5^{Ab}	99.65 ± 1.9^{Ab}	98.86 ± 2.3^{Ab}	97.7 ± 4.1^{Ab}
Diabetic plus Saline	Oral	100.0 ± 0.0^{A}	111.9 ± 6.3^{Abc}	120.5 ± 8.8^{ABCc}	130.33 ± 13.0^{BCDc}	143.5 ± 22.4^{BCc}	152.9 ± 24.6^{Dc}
	IP	100.0 ± 0.0^{A}	111.7 ± 5.2^{ABb}	123.1 ± 10.1^{ABCc}	137.1 ± 20.9^{BCDc}	148.8 ± 18.9^{BCc}	166.1 ± 21.3^{Dc}
Diabetic plus Gliben/insulin	Oral	100.0 ± 0.0^{C}	75.2 ± 9.4^{Ba}	66.4 ± 9.7^{Ba}	53.8 ± 10.2^{BCa}	40.4 ± 8.5^{Aa}	53.9 ± 14.8^{BCa}
	IP	100.0 ± 0.0^{C}	41.9 ± 5.2^{ABa}	36.5 ± 5.7^{ABc}	36.1 ± 5.8^{ABa}	35.2 ± 6.7^{Aa}	50.6 ± 11.7^{Ba}
mg/kg body weight							
25	Oral	100.0 ± 0.0^{D}	86.9 ± 6.0^{CDab}	75.0 ± 9.1^{BCab}	65.7 ± 8.9^{ABab}	51.1 ± 5.5^{Aa}	62.79 ± 7.3^{ABa}
	IP	100.0 ± 0.0^{B}	42.2 ± 3.3^{Aa}	38.6 ± 4.7^{Aa}	40.2 ± 10.7^{Aa}	38.5 ± 3.1^{Aa}	36.06 ± 3.6^{Aa}
48.4	Oral	100.0 ± 0.0^{D}	81.0 ± 6.6^{Aa}	64.0 ± 6.1^{Aa}	55.1 ± 9.3^{Aa}	45.0 ± 7.2^{Aa}	70.39 ± 13.4^{Aa}
	IP	100.0 ± 0.0^{B}	34.7 ± 5.7^{Aa}	33.9 ± 6.5^{Aa}	32.0 ± 6.8^{Aa}	38.3 ± 10.4^{Aa}	30.46 ± 6.6^{Aa}
93.5	Oral	100.0 ± 0.0^{E}	78.7 ± 2.5^{Da}	56.6 ± 3.6^{Ca}	45.9 ± 2.4^{Ba}	35.1 ± 5.3^{Aa}	71.39 ± 9.1^{Da}
	IP	100.0 ± 0.0^{B}	42.4 ± 8.3^{Aa}	35.6 ± 5.8^{Aa}	32.9 ± 5.3^{Aa}	33.2 ± 4.7^{Aa}	31.18 ± 8.7^{Aa}
180.9	Oral	100.0 ± 0.0^{D}	80.6 ± 9.3^{Ca}	66.1 ± 9.7^{BCa}	56.0 ± 10.1^{ABa}	43.8 ± 14.0^{Aa}	64.36 ± 4.5^{BCa}
	IP	100.0 ± 0.0^{B}	50.0 ± 24.6^{Aa}	35.6 ± 11.5^{Aa}	32.4 ± 10.1^{Aa}	30.9 ± 9.9^{Aa}	27.00 ± 7.2^{Aa}
350	Oral	100.0 ± 0.0^{D}	85.7 ± 13.1^{CDab}	71.5 ± 12.4^{BCa}	54.4 ± 15.0^{ABa}	37.0 ± 7.6^{Aa}	59.89 ± 9.0^{ABa}
	IP	100.0 ± 0.0^{B}	39.2 ± 8.1^{Aa}	$29.4\pm8.2A^{a}$	26.7 ± 3.9^{Aa}	25.2 ± 6.9^{Aa}	29.1 ± 10.3^{Aa}

Values expressed as Means ± SD for five animals per group. Means within respective rows followed by similar upper case letters are not significantly different at $\rho \leq 0.05$ while values in columns followed by similar lower case letters are not significantly different at $\rho \leq 0.05$.

Appendix 4: Percent change in glucose levels after oral and intraperitoneal administration of *M. undata* at various doses to alloxan induced mice

Treatment	Route	%Glucose levels at different hours after treatment					
		0	2	4	6	8	24
Normal control	Oral	100.0 ± 0.0^{A}	98.1 ± 2.12^{Aab}	99.2 ± 0.9^{Acd}	95.8 ± 4.2^{Ab}	98.5 ± 2.5^{Ab}	100.5 ± 4.0^{Ab}
	IP	100.0 ± 0.0^{A}	100.1 ± 1.2^{Ab}	100.0 ± 1.2^{Ab}	100.8 ± 1.5^{Ab}	100.8 ± 2.6^{Ab}	99.3 ± 2.3^{Ab}
Diabetic plus Saline	Oral	100.0 ± 0.0^{A}	117.0 ± 8.0^{ABb}	131.7 ± 12.8^{ABd}	144.3 ± 13.1^{BCc}	152.2 ± 13.5^{BCc}	157.7 ± 14.8^{Cc}
	IP	100.0 ± 0.0^{A}	113.0 ± 3.9^{ABb}	122.8 ± 3.9^{BCb}	131.8 ± 10.2^{CDc}	143.6 ± 10.7^{DEc}	157.6 ± 10.7^{Ec}
Diabetic plus Gliben/insulin	Oral	100.0 ± 0.0^{A}	76.6 ± 5.2^{Aab}	52.2 ± 1.6^{Aa}	39.6 ± 3.3^{Aa}	28.9 ± 3.9^{Aa}	38.7 ± 6.1^{Aa}
	IP	100.0 ± 0.0^{C}	45.4 ± 3.1^{ABa}	42.8 ± 3.1^{ABa}	40.3 ± 3.7^{ABa}	38.9 ± 4.7^{Aa}	47.5 ± 5.3^{Ba}
mg/kg body weight							
25	Oral	100.0 ± 0.0^{A}	97.2 ± 16.5^{ABab}	94.4 ± 32.7^{ABbc}	93.3 ± 42.8^{BCb}	93.2 ± 50.5^{BCb}	99.0 ± 48.6^{Cbc}
	IP	100.0 ± 0.0^{B}	72.8 ± 33.6^{ABab}	46.3 ± 33.6^{Aa}	35.0 ± 14.2^{Aa}	29.8 ± 10.5^{Aa}	72.4 ± 30.9^{Bab}
48.4	Oral	100.0 ± 0.0^{E}	74.0 ± 25.0^{Dab}	62.3 ± 25.0^{Cabc}	53.8 ± 25.1^{ABa}	50.0 ± 23.9^{Aa}	$77.9\pm21.1B^{Cab}$
	IP	100.0 ± 0.0^{B}	85.7 ± 33.7^{ABab}	62.1 ± 33.7^{Aa}	46.5 ± 17.5^{Aa}	36.5 ± 5.1^{Aa}	92.9 ± 45.7^{ABab}
93.5	Oral	100.0 ± 0.0^{B}	92.6 ± 15.8^{ABab}	88.0 ± 28.4^{ABabc}	85.4 ± 36.7^{ABa}	84.6 ± 42.8^{Aa}	94.8 ± 38.6^{ABab}
	IP	100.0 ± 0.0^{B}	50.7 ± 14.1^{ABa}	39.9 ± 5.2^{ABa}	$34.4\pm2.5^{AB}a$	30.5 ± 3.1^{Aa}	56.5 ± 4.5^{ABab}
180.9	Oral	100.0 ± 0.0^{C}	91.5 ± 15.6^{BCab}	85.7 ± 27.8^{BCabc}	83.3 ± 36.4^{ABab}	81.8 ± 42.2^{Aa}	93.6 ± 38.5^{BCab}
	IP	100.0 ± 0.0^{D}	52.4 ± 9.4^{BCa}	42.7 ± 5.1^{ABa}	39.4 ± 3.2^{Aa}	35.4 ± 5.7^{Aa}	60.2 ± 6.3^{Cab}
350	Oral	100.0 ± 0.0^{A}	86.4 ± 9.3^{Aa}	76.5 ± 16.3^{Aab}	71.1 ± 20.7^{Aa}	$67.7\pm24.3^{A}a$	80.8 ± 22.2^{Aab}
	IP	100.0 ± 0.0^{B}	50.5 ± 7.1^{Aa}	38.8 ± 11.4^{Aa}	38.1 ± 11.6^{Aa}	35.8 ± 8.4^{Aa}	47.7 ± 13.2^{Aa}

Values expressed as Means ± SD for five animals per group. Means within respective rows followed by similar upper case letters are not significantly different at $\rho \leq 0.05$ while values in columns followed by similar lower case letters are not significantly different at $\rho \leq 0.05$.

Appendix 5: Percent change in glucose levels after oral and intraperitoneal administration of *S. cordatum* at various doses to alloxan induced mice

Treatment	Route	%Glucose levels at different hours after treatment					
		0	2	4	6	8	24
Normal control	Oral	100.0 ± 0.0^{A}	$101.2\pm1.6b^{Ac}$	101.6 ± 2.0^{Abc}	100.8 ± 2.0^{Ac}	102.8 ± 2.0^{Ac}	102.8 ± 2.7^{Ab}
	IP	100.0 ± 0.0^{A}	101.6 ± 0.8^{Ac}	102.4 ± 1.49^{Ac}	102.4 ± 1.93^{Ac}	100.8 ± 1.56^{Ad}	102.0 ± 2.2^{Ab}
Diabetic plus Saline	Oral	100.0 ± 0.0^{A}	120.5 ± 10.3^{Abc}	134.5 ± 22.5^{ABc}	146.9 ± 23.9^{ABd}	160.2 ± 32.0^{Bd}	169.3 ± 34.0^{Bc}
	IP	100.0 ± 0.0^{A}	120.1 ± 8.1^{Abc}	130.3 ± 7.3^{BCd}	149.8 ± 13.7^{CDd}	170.4 ± 10.9^{DEe}	188.1 ± 12.6^{Ec}
Diabetic plus Gliben/insulin	Oral	100.0 ± 0.0^{D}	74.0 ± 7.1^{Cab}	54.7 ± 9.3^{Ba}	34.9 ± 4.4^{Aa}	28.1 ± 5.2^{Aa}	41.0 ± 6.9^{Aa}
	IP	100.0 ± 0.0^{D}	50.77 ± 3.2^{Ba}	46.1 ± 3.0^{ABab}	43.2 ± 4.2^{Ab}	42.9 ± 4.4^{Ac}	61.0 ± 2.6^{Cab}
mg/kg body weight							
25	Oral	100.0 ± 0.0^{A}	92.4 ± 19.0^{Aabc}	100.8 ± 19.5^{Abc}	93.0 ± 17.9^{Abc}	87.08 ± 22.65^{Abc}	103.7 ± 15.1^{Ab}
	IP	100.0 ± 0.0^{B}	45.6 ± 13.6^{Aa}	29.7 ± 11.9^{Aa}	23.1 ± 8.3^{Aa}	16.18 ± 8.08^{Aa}	57.3 ± 41.5^{Aa}
48.4	Oral	100.0 ± 0.0^{C}	97.2 ± 15.1^{Cabc}	82.1 ± 20.3^{Cab}	50.7 ± 9.1^{ABa}	37.83 ± 15.91^{Aa}	74.5 ± 13.7^{BCab}
	IP	100.0 ± 0.0^{B}	42.1 ± 9.4^{Aa}	33.9 ± 8.2^{Aa}	30.3 ± 11.9^{Aab}	25.25 ± 10.23^{Aab}	87.7 ± 20.9^{Aab}
93.5	Oral	100.0 ± 0.0^{C}	69.9 ± 11.3^{Ba}	56.0 ± 14.0^{ABa}	49.1 ± 11.8^{ABa}	37.63 ± 9.53^{Aa}	65.6 ± 14.3^{Ba}
	IP	100.0 ± 0.0^{C}	37.2 ± 4.6^{Ba}	33.4 ± 3.2^{ABa}	26.7 ± 3.9^{Aab}	29.32 ± 1.49^{ABabc}	101.7 ± 7.5^{Cab}
180.9	Oral	100.0 ± 0.0^{D}	78.9 ± 13.1^{Cab}	56.5 ± 11.8^{ABa}	45.6 ± 10.3^{Aa}	37.64 ± 5.79^{Aa}	68.5 ± 7.8^{BCab}
	IP	100.0 ± 0.0^{D}	79.4 ± 7.5^{Cb}	57.3 ± 13.2^{ABb}	45.5 ± 10.0^{Ab}	39.85 ± 6.99^{Abc}	69.5 ± 8.3^{CDab}
350	Oral	100.0 ± 0.0^{C}	89.9 ± 19.5^{BCab}	75.6 ± 14.1^{ABCab}	62.7 ± 14.8^{ABab}	55.90 ± 13.20^{Aab}	70.4 ± 8.4^{ABab}
	IP	100.0 ± 0.0^{B}	40.3 ± 6.4^{Aa}	36.7 ± 6.9^{Aa}	31.3 ± 6.4^{Aab}	25.73 ± 6.89^{Aab}	91.0 ± 23.6^{Bab}

Values expressed as Means ± SD for five animals per group. Means within respective rows followed by similar upper case letters are not significantly different at $\rho \leq 0.05$ while values in columns followed by similar lower case letters are not significantly different at $\rho \leq 0.05$.

Appendix 6: Percent change in glucose levels after oral and intraperitoneal administration of *M. subcordata* at various doses to alloxan induced mice

Treatment	Route	%Glucose levels at different hours after treatment					
		0	2	4	6	8	24
Normal control	Oral	100.0 ± 0.0^{A}	99.7 ± 2.1^{Aa}	99.3 ± 3.5^{Aabc}	99.3 ± 2.6^{Abc}	99.7 ± 2.1^{Abc}	102.0 ± 4.2^{Aa}
	IP	100.0 ± 0.0^{A}	101.2 ± 1.7^{Ac}	100.4 ± 2.5^{Acd}	101.2 ± 2.2^{Ac}	101.6 ± 2.5^{Ac}	99.6 ± 2.5^{Ab}
Diabetic plus Saline	Oral	100.0 ± 0.0^{A}	106.1 ± 3.8^{ABab}	112.4 ± 4.6^{ABbc}	121.6 ± 10.1^{BCc}	127.1 ± 12.9^{BCc}	140.9 ± 20.3^{Ca}
	IP	100.0 ± 0.0^{A}	111.0 ± 3.4^{Bc}	121.1 ± 5.9^{BCd}	130.9 ± 6.6^{Cd}	144.4 ± 2.7^{Dd}	159.1 ± 6.3^{Ec}
Diabetic plus Gliben/insulin	Oral	100.0 ± 0.0^{A}	71.8 ± 8.6^{Aa}	55.7 ± 4.7^{Aa}	40.6 ± 6.0^{Aa}	26.6 ± 5.2^{Aa}	43.1 ± 13.1^{Aa}
	IP	100.0 ± 0.0^{D}	34.7 ± 1.7^{Ba}	33.6 ± 2.5^{ABa}	30.8 ± 1.1^{ABa}	29.4 ± 0.9^{Aa}	47.3 ± 4.7^{Ca}
mg/kg body weight							
25	Oral	100.0 ± 0.0^{A}	89.2 ± 40.2^{ABa}	71.0 ± 29.6^{ABab}	61.9 ± 27.6^{BCab}	51.6 ± 9.3^{BCab}	95.2 ± 14.4^{Ca}
	IP	100.0 ± 0.0^{B}	61.8 ± 17.4^{Aab}	49.5 ± 13.8^{Aab}	46.4 ± 14.5^{Aab}	41.8 ± 16.0^{Aab}	69.6 ± 23.5^{ABab}
48.4	Oral	100.0 ± 0.0^{E}	81.5 ± 1.2^{Da}	66.4 ± 12.3^{Cab}	67.6 ± 13.9^{ABab}	56.0 ± 13.5^{Aab}	84.3 ± 5.8^{BCa}
	IP	100.0 ± 0.0^{B}	83.4 ± 24.4^{ABbc}	69.1 ± 14.9^{ABb}	62.6 ± 11.6^{Ab}	59.6 ± 10.2^{Ab}	93.8 ± 22.5^{ABb}
93.5	Oral	100.0 ± 0.0^{B}	153.4 ± 51.2^{ABb}	133.1 ± 58.0^{Abc}	115.3 ± 49.0^{ABbc}	89.1 ± 52.1^{Abc}	142.3 ± 33.1^{ABa}
	IP	100.0 ± 0.0^{C}	80.2 ± 17.5^{BCbc}	71.2 ± 13.6^{ABb}	61.4 ± 12.5^{Ab}	50.0 ± 12.8^{Aab}	75.0 ± 13.0^{ABCab}
180.9	Oral	100.0 ± 0.0^{C}	104.5 ± 21.5^{BCab}	88.6 ± 28.5^{BCabc}	78.7 ± 28.1^{ABabc}	61.1 ± 21.8^{Aab}	113.6 ± 43.4^{BCb}
	IP	100.0 ± 0.0^{D}	81.6 ± 8.2^{Cbc}	$74.9\pm11.2B^{Cbc}$	59.7 ± 12.5^{ABab}	48.1 ± 5.3^{Aab}	75.1 ± 10.5^{BCab}
350	Oral	100.0 ± 0.0^{A}	80.6 ± 20.2^{Aa}	72.3 ± 26.0^{Aab}	74.3 ± 34.0^{Aabc}	63.1 ± 36.4^{Aab}	82.5 ± 19.8^{Ac}
	IP	100.0 ± 0.0^{C}	71.2 ± 14.0^{ABCab}	58.9 ± 14.0^{ABab}	59.3 ± 20.6^{ABab}	52.5 ± 13.1^{Aab}	$83.\pm10.6^{BCab}$

Values expressed as Means ± SD for five animals per group. Means within respective rows followed by similar upper case letters are not significantly different at $\rho \leq 0.05$ while values in columns followed by similar lower case letters are not significantly different at $\rho \leq 0.05$.

Appendix 7: Percent change in glucose levels after oral and intraperitoneal administration of *P. capensis* at various doses to alloxan induced mice.

Treatment	Route	%Glucose levels at different hours after treatment					
		0	2	4	6	8	24
Normal control	Oral	100.0 ± 0.0^{A}	99.6 ± 1.9^{Aab}	98.9 ± 3.4^{Aab}	102.0 ± 3.9^{Aab}	100.4 ± 2.3^{Aab}	99.6 ± 2.2^{Aa}
	IP	100.0 ± 0.0^{A}	101.2 ± 1.6^{Ac}	101.2 ± 2.9^{Bb}	101.2 ± 8.1^{Ab}	101.6 ± 8.1^{Ab}	101.2 ± 2.4^{Ab}
Diabetic plus Saline	Oral	100.0 ± 0.0^{A}	117.6 ± 7.3^{ABb}	132.3 ± 15.0^{Bb}	140.7 ± 16.4^{BCb}	146.7 ± 18.3^{BCb}	151.9 ± 21.2^{Ca}
	IP	100.0 ± 0.0^{A}	116.2 ± 7.4^{Abc}	125.5 ± 8.4^{ABc}	135.3 ± 10.3^{BCc}	151.1 ± 10.5^{CDc}	162.8 ± 11.6^{Dc}
Diabetic plus Gliben/insulin	Oral	100.0 ± 0.0^{D}	75.3 ± 11.6^{Cab}	51.0 ± 7.6^{ABa}	38.9 ± 8.2^{ABa}	30.6 ± 6.8^{Aa}	38.0 ± 7.8^{ABa}
	IP	100.0 ± 0.0^{C}	108.7 ± 7.4^{ABa}	113.4 ± 12.1^{BCa}	118.3 ± 17.0^{Aa}	126.4 ± 24.8^{Aa}	132.0 ± 30.8^{Ba}
mg/kg body weight							
25	Oral	100.0 ± 0.0^{A}	96.4 ± 11.5^{Aab}	90.9 ± 11.9^{Aab}	82.9 ± 6.4^{Aab}	82.9 ± 8.1^{Aab}	82.82 ± 8.87^{Aab}
	IP	100.0 ± 0.0^{E}	82.3 ± 8.4^{Db}	65.2 ± 6.3^{BCb}	53.4 ± 6.0^{ABb}	47.5 ± 7.0^{Ab}	73.1 ± 8.1^{Db}
48.4	Oral	100.0 ± 0.0^{A}	85.8 ± 13.3^{Aab}	76.0 ± 13.4^{Aab}	72.4 ± 18.5^{Aab}	81.4 ± 20.7^{Aab}	69.3 ± 11.3^{Aab}
	IP	100.0 ± 0.0^{D}	78.4 ± 8.9^{Cb}	64.3 ± 12.2^{BCb}	51.6 ± 5.6^{ABb}	43.7 ± 3.1^{Ab}	58.7 ± 7.9^{ABb}
93.5	Oral	100.0 ± 0.0^{A}	92.1 ± 14.8^{Aab}	86.4 ± 14.2^{Aab}	78.0 ± 9.3^{Aab}	86.1 ± 5.8^{Aab}	102.2 ± 14.0^{Aab}
	IP	100.0 ± 0.0^{D}	92.6 ± 14.8^{CDb}	85.5 ± 14.2^{ABCb}	80.3 ± 9.3^{ABb}	84.2 ± 5.8^{Ab}	84.6 ± 14.0^{CDb}
180.9	Oral	100.0 ± 0.0^{B}	88.4 ± 10.6^{BCab}	65.0 ± 19.0^{BCab}	75.8 ± 16.2^{BCab}	69.0 ± 11.7^{Aab}	68.7 ± 11.7^{Aab}
	IP	100.0 ± 0.0^{D}	72.5 ± 3.6^{Cb}	52.1 ± 10.5^{ABb}	43.8 ± 9.1^{Ab}	37.7 ± 5.8^{Ab}	67.8 ± 9.9^{BCb}
350	Oral	100.0 ± 0.0^{A}	48.6 ± 21.6^{Aa}	59.8 ± 31.1^{Aab}	61.5 ± 60.0^{Aab}	78.2 ± 32.6^{Aab}	101.3 ± 13.8^{Aab}
	IP	100.0 ± 0.0^{D}	82.2 ± 7.9^{Cb}	80.9 ± 12.7^{ABCb}	74.1 ± 9.5^{ABb}	79.7 ± 9.9^{Ab}	87.8 ± 14.9^{BCb}

Values expressed as Means ± SD for five animals per group. Means within respective rows followed by similar upper case letters are not significantly different at $\rho \leq 0.05$ while values in columns followed by similar lower case letters are not significantly different at $\rho \leq 0.05$.

Appendix 8: Photo of *Chasmanthera dependens*:

Photograph taken in Sept. 2014 in Songita along Kerio valley

Appendix 9: Approval of research proposal

KENYATTA UNIVERSITY
GRADUATE SCHOOL

E-mail: dean-graduate@ku.ac.ke
Website: www.ku.ac.ke
P.O. Box 43844, 00100
NAIROBI, KENYA
Tel. 810901 Ext. 57530

Internal Memo

FROM: Dean, Graduate School DATE: 20th May, 2014

TO: Dinah J. Sawe
C/o Biochemistry and Biotechnology
Dept. REF: I56/25195/2011

SUBJECT: APPROVAL OF RESEARCH PROPOSAL

This is to inform you that Graduate School Board, at its meeting of 15th January, 2014, approved your Research Proposal for the M.Sc Degree Entitled, "In *Vivo* Hypoglycemic Activity and Safety of Selected Medicinal Plants used in the Management of Diabetes Mellitus in Elgeiyo-Marakwet County, Kenya."

Thank you.

DAVID NJOROGE
FOR: DEAN, GRADUATE SCHOOL

c.c. Chairman, Department of Biochemistry and Biotechnology

Supervisors:

1. Prof. Elind NM Njagi
C/o Department of Biochemistry and Biotechnology
Kenyatta University

2. Dr. Alice N. Muchugi
C/o Department of Biochemistry and Biotechnology
Kenyatta University

3. Prof. Peter K. Gathumbi
C/o Department of Veterinary, Pathology and Microbiology
College of Agriculture and Veterinary Services
University of Nairobi
P.O BOX 29053-00625
NAIROBI

Appendix 10: Research Authorization

KENYATTA UNIVERSITY
GRADUATE SCHOOL

E-mail: dean-graduate@ku.ac.ke
Website: www.ku.ac.ke

P.O. Box 43844, 00100
NAIROBI, KENYA
Tel. 8710901 Ext. 57530

Our Ref: I56/25195/11

DATE: 20th May, 2014

The Permanent Secretary,
Ministry of Higher Education, Science & Technology,
P.O. Box 30040,
NAIROBI

Dear Sir/Madam,

RE: RESEARCH AUTHORIZATION DINAH J. SAWE – REG. NO. I56/25195/11

I write to introduce Ms. Dinah J. Sawe who is a Postgraduate Student of this University. She is registered for M.Sc degree programme in the **Department of Biochemistry and Biotechnology.**

Ms. Sawe intends to conduct research for a M.Sc proposal entitled, **"In *Vivo* Hypoglycemic Activity and Safety of Selected Medicinal Plants used in the Management of Diabetes Mellitus in Elgeiyo-Marakwet County, Kenya."**

Any assistance given will be highly appreciated.

Yours faithfully,

for MRS. LUCY N. MBAABU
FOR: DEAN, GRADUATE SCHOOL

Appendix 11: Authority to use animal house

KENYATTA UNIVERSITY
SCHOOL OF PURE AND APPLIED SCIENCE
DEPARTMENT OF BIOCHEMISTRY AND BIOTECHNOLOGY

INTERNAL MEMO

From: Chairman **Date:** 24th September, 2013

To: Animal house

Re: Dinah J. Sawe I56/25195/2011

The above named student has been allowed to conduct her research project in the animal house.

Thank you.

DEPARTMENT OF BIOCHEMISTRY & BIOTECHNOLOGY
24 SEP 2013
KENYATTA UNIVERSITY

Dr. D. N. Mburu
Chairman, Department of Biochemistry and Biotechnology