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Role of Ethanolic Cabbage Extract on Blood Glucose Level and Liver Function of Alloxan Induced Diabetic of Male Wistar Rat

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ABSTRACT

Plants in folklore medicine has shown to posse's antidiabetic and hepatoprotective tendencies, owing to the facts that most plant material contains phytochemical which can be therapeutically employed in the management of different pathological conditions. A total of 36 male wistar rat was used for this study, and the animal where divided into six groups of six animal, Group 1: (positive control): Normal rats received only feed and distilled water for three weeks. Group 2:(Negative control): Diabetic rats which received only feed and water. Group 3: In this group, diabetic rats were induced with 150mg/kg of alloxan and treated with low dose of extract (cabbage extract - 150mg/kg) for 3 weeks. Group 4: In this group, diabetic rats were induced with 150mg/kg of alloxan and treated with medium dose of extract (cabbage extract- 300mg/kg) for 3 weeks Group 5: In this group, diabetic rats were induced with 150mg/kg of alloxan and treated with high dose of extract (cabbage extract - 600mgkg).Group 6: In this group, normal rats received high dose of extract (cabbage extract - 600mg/kg) for two weeks before it was induced diabetes 150mg/kg. The results obtained from this study demonstrated that cabbage supplementation reduced the high blood sugar levels as observed in diabetic rats in this study. The present study also indicated a marked increase in the ALP levels which is suggesting an adverse effect of cabbage on the liver, therefore there is the need for more study on the toxicological profile of cabbage on the liver.

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1. INTRODUCTION

1.1. Background of the Study

Diabetes is a devastating non-communicable disease that occurs due to the failure of the pancreas to produce enough insulin or when the body cannot use the insulin it produces effectively (World Health Organization, 2017). Diabetes Mellitus (DM) is a global health care menace that may reach pandemic levels by 2030 (Abougalambou *et al.,* 2016). About 80% of the total adult diabetics are in developing countries and the greatest concern is the growing incidence of Type 2 Diabetes at a younger age including some obese children even before puberty affecting the productive years of their lives (Tabish, 2017).

Diabetes is a disease which affects the metabolism of carbohydrates, proteins, and fat due to absolute or relative deficiency of insulin secretion with or without varying degree of insulin resistance (Asadujjaman *et al*., 2016). The number of individuals with diabetes has been increasing due to population growth, aging, urbanization, and increasing prevalence of obesity and physical inactivity (Samec *et al*., 2016). The World Health Organization (WHO) estimated the diabetic population to increase up to 300 million or more by the year 2025 (Patel *et al.,* 2016). The most important distinctive feature of diabetes is an elevated blood glucose concentration, but this abnormality is just one of a number of biochemical and physiological changes that occur (Olaitan, 2015). Hypercholesterolemia and hyper triglyceridemia are common complications of diabetes mellitus (Akhtar *et al*., 2007).

The treatment of diabetes mainly involves the use of hypoglycaemic drugs in addition to insulin but the unwanted side effects of these drugs prompted a

demand for new compounds for the treatment of diabetes (Asadujjaman *et al*., 2016). The drive for change from orthodox to herbal medicines is to an extent due to the adverse reactions, undesirable side effects of synthetic drugs, the cost of buying modern antidiabetic drugs, which is beyond the reach of the lower class citizens and the belief that natural products are safer to the biological systems (Mohammed *et al*., 2007). It has now become necessary to search for new compounds in order to overcome these problems, and several traditional medicines are now used to manage diabetes mellitus in different societies all over the continents (Raju *et al*., 2011).

Cabbage (*Brassica oleracea*) is locally called *Kabeji* in Hausa language and *Akojopo* or *Jaleji* in Yoruba language. It is an important vegetable crop of the *Brassicaceae* family consumed all over the world. It is popular probably due to its low price and availability at local markets, richness in phytochemicals such as polyphenolics, glucosinolates, carotenoids, and vitamin C. It has demonstrated antioxidant, anticancer and potential anti-obesity properties (Dheer & Bhatnagar, 2014). It consists of a wide range of important vegetable and fodder crops which are excellent sources of fibers that help prevents constipation, reduces the risk of colorectal cancer and helps to reduce blood sugar and blood cholesterol levels, thereby reducing the risk of heart disease. Diabetes (Enas & Atif, 2015). Ethanolic extract of cabbage, has demonstrated significant hepatoprotective activity which justifies its use as a hepato protective agent as a result of the presence of biologically active phytoconstituents (Subramanian, 2017).

1.2. Statement of the Problem

Diabetes mellitus is a global health problem which affects an estimated population of 135 million in 1995 and the number being expected to rise to about 300 million in the year 2025 with more people in developing than developed countries (Baltazar *et al.*, 2018). Insulin and oral hypoglycemic drugs such as sulfonylureas and biguanides have remained the corner stone for the management of diabetes mellitus. Unfortunately, apart from having a number of side effects, none of the oral synthetic hypoglycemic agents has been successful in maintaining euglycaemia. The use of medicinal plants for the treatment of diabetes mellitus has gained recognition and recommendation by the World Health Organization (WHO), especially in developing countries where access to the conventional treatment are expensive and not readily accessible.

1.3. Aim of the Study

To determine the role of cabbage (brassica olaeracae) extract on blood glucose, liver functions and the body weight.

1.4. Specific Objectives

1. To determine the effects of cabbage extract on body weight.
2. To determine the effects of cabbage extract on liver function (ALP, AST,ALT).
3. To determine the effects of cabbage extract on blood glucose level.

1.5. Significance of the Study

The findings of this study will be significant to health practitioners and the general public as a whole. The findings of this study will serve as a guide and an eye opener to beneficiaries on the role of cabbage (brassica olaeracae) extract on blood glucose, liver function and body weight in alloxan induced diabetic wistar rats. More than four hundred different plant and plant extracts have been found to play an important role in the treatment of diabetes and most of these plants were believed to have hypoglycaemic properties. Cabbage is one of such medicinal plants, whose therapeutic application has a folkloric background. The plant enjoys widespread reputation as a remedy for peptic ulcer disease, hypocholeterolaemic, anti-cancer, antimicrobial and anti-inflammatory properties (Sathya, 2012). A scientific verification of its use as an extract would be important in establishing a pharmacological basis for some of the claimed ethnomedicinal uses of the plant. This scientific verification forms the basis of the present investigation using animal models.

1.6. Scope of the Study

This study is delimited to assessing the role of cabbage (brassica olaeracae) extract on blood glucose and some physiological parameters in alloxan induced diabetic wistar rats. The study was designed to investigate the effect of cabbage extract on body weight, blood glucose and liver function test on alloxan induced diabetic Wistar rats.

2. LITERATURE REVIEW

2.1. Concept of Diabetes Mellitus (DM)

Diabetes Mellitus (DM) is a global health care menace that may reach pandemic levels by 2030 (Abougalambou *et al.,* 2016). About 80% of the total adult diabetics are in developing countries and the greatest concern is the growing incidence of Type 2 Diabetes at a younger age including some obese children even before puberty affecting the productive years of their lives (Tabish, 2017). Considerable evidence has seen diabetes changing into an epidemic in many developing countries with an estimated prevalence of diabetes of 1% in rural areas of Africa

and prevalence in Nigeria ranging from 0.65% in rural Mangu in the North to 11% in urban Lagos in the Southern part of the country (Chinenye and Young 2015; Mutlu, *et al.,* 2017). Diabetes mellitus is a disease that is waging war against the wellbeing of humans and may probably be due to drastic lifestyle changes accompanying urbanization and westernization in developing countries (Harande, 2015). Individuals with diabetes are more likely to be hospitalized with cardiovascular disease, end stage renal disease and most frequently, non-traumatic lower limb amputation compared to the general population (Cheng, 2017).

Diabetes mellitus is a chronic and complex metabolic disease that has deleterious effects on multiple organ system (Bhuva & Addepalli, 2015). It is an endocrine-metabolic disorder characterized by chronic hyperglycaemia secondary to relative or absolute lack of insulin giving rise to the risk of microvascular and macrovascular damage, with associated reduced life expectancy and diminished quality of life (Chinenye & Young, 2015). Several disease mechanisms are involved in the development of diabetes mellitus ranging from autoimmune destruction of the β-cells of the pancreas to abnormalities that result in resistance to insulin action. However of recent, strong evidence has shown that both type-1 diabetes and type-2 diabetes are now caused by the formation of tiny toxic clumps of the hormone amylin, produced by the beta cells of the pancreas which in turn destroys the pancreatic beta cells leading to the development of diabetes (Zhang *et al.,* 2018).

2.2. Types of Diabetes Mellitus

2.2.1. Type 1 diabetes mellitus

Type 1 diabetes mellitus (T1DM) is present in about 5–10% of people having diabetes with a strong genetic linkage inherited mainly through the HLA complex (Daneman, 2016). An autoimmune disease mediated by T lymphocytes which cause a progressive destruction of the pancreatic beta cells (Dip & Gomez, 2014). A large number people with T1DM are youths, amounting to ≥85% of all diabetes cases in youth < 20 years of age and individuals diagnosed with T1DM when they are adults have been referred to as having latent autoimmune diabetes of adults (Maahs *et al.,* 2015). Those with T1DM have increased risk of other autoimmune disorders like autoimmune thyroid and celiac diseases while complications like nephropathy may result into hypercalciuria which can alter vitamin D metabolism leading to vitamin D deficiency and consequently osteoporosis (Dhaon & Shah, 2017). The genetic basis of T1DM is not yet fully understood. However, genetic determinants such as alleles of the major histocompatibility locus (HLA) at the HLA-DRB1 and DQB1 loci and it has been discovered that HLA-B*39 locus account for some 40–50% of the familial clustering of T1DM (Forbes & Cooper, 2018).

2.2.2. Type 2 diabetes mellitus

Type 2 Diabetes Mellitus is a chronic metabolic disease caused by impaired glucose tolerance due to insulin resistance and consequential islet β-cell exhaustion, resulting to insulin deficiency (Badawi *et al.,* 2016). It is the most common type of diabetes affecting about 85-90% of all people with older adults usually affected. Younger populations are also now increasingly being diagnosed with Type 2 diabetes, having about 45% of new cases of Type 2 diabetes mellitus in the paediatric population (Jordan and Jordan, 2012). Genetic and environmental factors play a role in the aetiology of Type 2 diabetes and the risk is greatly increased with change in lifestyle factors such as high blood pressure, obesity, lack of exercise and poor diet (Hu *et al.,*2007). It is still not established whether genetic factors or aging can explain the rapid increase in the prevalence of Type 2 Diabetes (Forbes & Cooper, 2013).

2.2.3. Maturity onset of diabetes of the young (MODY)

Maturity onset of diabetes of the young (MODY) is a form of diabetes that is caused by mutations in a number of different genes. It has now been discovered that there are at least six forms of MODY (MODY 1- 6), each with mutation in a different gene that is directly involved with beta cell function (Winter, 2003).Those who carry MODY2 mutations have a very mild form of the disease, while those who carry MODY1 and MODY3 variants have a much more severe expression that is associated with long-term complications (Pearson *et al.,* 2010). MODY, is inherited as an autosomal dominant trait resulting from mutations in glucokinase gene on chromosome 7p.This condition is diagnosed as hyperglycemia before the age of twenty-five years and treatable for over five years without insulin in cases where islet cell antibodies are negative and HLA-DR3 and DR4 are heterozygous. MODY is more common in blacks and Indians seen in more than 10% of diabetics but rare in Caucasians having a prevalence of less than 1% (Ozougwu *et al.,* 2016).

2.2.4. Gestational diabetes

Gestational diabetes mellitus (GDM) is defined by glucose intolerance diagnosed first at any time during pregnancy. This condition is found to be associated with various prenatal and maternal complications ranging from neonatal hypoglycemia, macrosomia, jaundice, hypocalcaemia and polycythemia with an

increased frequency of maternal hypertensive disorders leading to an increased rate of caesarean delivery (Linsay, 2014).

2.2.5. Neonatal diabetes

Neonatal diabetes mellitus (NDM) is defined as hyperglycaemia requiring insulin treatment occurring in the first 6 months of life (Kataria, 2017). Neonatal diabetes mellitus is considered a rare disease affecting one in 300,000 to 400,000 newborns (Grulich-Henn *et al.,* 2015). It is classified as transient NDM (TNDM) and permanent NDM (PNDM) with TNDM, accounting for 50% to 60% of all NDM cases, requires initial insulin treatment but appears to resolve spontaneously by a median of 12 weeks of age, only to relapse years later (Kataria, 2017). Permanent NDM is less common and is also characterized by early hyperglycaemia. However, unlike TNDM, PNDM has no period of remission and must be treated lifelong. Unlike autoimmune diabetes, which is extremely rare before 6 months of age, NDM is a monogenic form of diabetes, with insulinopenia resulting from abnormal pancreatic islet development, decreased β -cell mass, or -cell β dysfunction (Aguilar-Bryan & Bryan, 2014).

2.2.6. Pathogenesis of type 2 diabetes mellitus

Under normal physiological conditions, plasma glucose concentrations are maintained within a narrow range, despite wide fluctuations in supply and demand, through a tightly regulated and dynamic interaction between tissue sensitivity to insulin (especially in the liver) and insulin secretion (Moller and Flier, 1991). In type 2 diabetes these mechanisms break down, with the consequence that the two main pathophysiological defects in type 2 diabetes are impaired insulin secretion through a dysfunction of the pancreatic β-cell, and impaired insulin action through insulin resistance. Insulin resistance is now regarded as being synonymous with a reduced rate of whole-body insulin-mediated glucose disposal in insulin-sensitive tissues (Moller and Flier, 1991). This definition is too narrow, and insulin resistance may be better defined as existing when normal insulin concentrations fail to produce a normal biological response (Kahn, 1978).

The main advantage of the latter definition is that it does not restrict consideration of insulin action to a solitary aspect of intermediary metabolism. The importance of insulin actions on other aspects of intermediary metabolism, including lipid and protein metabolism, has now been appreciated. In 1988, Reaven described syndrome X (now commonly known as the metabolic syndrome or insulin resistance syndrome) as the association between several cardiovascular risk factors, including hypertension, dyslipidaemia and glucose intolerance, and he proposed that insulin resistance was the underlying cause (Reaven, 1988). Since his original description, it has been recognised that a significant proportion of patients with the metabolic syndrome do not have insulin resistance (Ford *et al,* 2012). The definition of the metabolic syndrome has therefore been modified: most notably, central obesity has been added as a core feature. This is important, as it is increasingly recognised that central obesity is fundamental to the origin of this disorder (Maison *et al*, 2010). Abnormalities in β-cell function are found early in the natural history of type 2 diabetes and in first-degree relatives of people with type 2 diabetes (Ford *et al,* 2012), suggesting that they are an integral component of the pathogenesis of type 2 diabetes.

2.3. Metabolic Syndrome

Metabolic syndrome (MetS) is defined by a group of interconnected physiological, biochemical, clinical, and metabolic factors that directly increases the risk of atherosclerotic cardiovascular disease (Kaur, 2017). Worldwide prevalence of MetS ranges from <10% to as much as 84%, depending on the region, urban or rural environment, composition of the population studied, and the definition of the syndrome used (Kaur, 2017). MetS is a state of chronic low grade inflammation as a consequence of complex interplay between genetic and environmental factors. Insulin resistance, visceral adiposity, atherogenic dyslipidemia, endothelial dysfunction, genetic susceptibility, elevated blood pressure, hypercoagulable state, and chronic stress are the several factors which constitute the syndrome.

2.4. Abdominal Obesity

Obesity is principally driven by an increased consumption calorie-dense food and reduced physical activity. Adipose tissue is a heterogeneous mix of adipocytes, stromal preadipocytes, immune cells, and endothelium, and it can respond rapidly and dynamically to alterations in nutrient excess through adipocytes hypertrophy and hyperplasia (Halberg *et al.,* 2016). Progressive adipocytes enlargement with obesity may lead to depletion of blood supply to the adipocytes which may consequently lead to hypoxia (Cinti *et al.,* 2015). Hypoxia has been proposed to be an inciting etiology of necrosis and macrophage infiltration into adipose tissue that leads to an overproduction of biologically active metabolites known as adipocytokines which includes glycerol, free fatty acids (FFA), proinflammatory mediators (tumour necrosis factor alpha (TNFα) and interleukin-6 (IL-6)), plasminogen activator inhibitor-1 (PAI-1), and C-reactive protein (CRP) (Lau *et al.,* 2005). This result in a localized inflammation in adipose tissue that propagates an overall systemic inflammation

associated with the development of obesity related comorbidities (Trayhurn and Wood, 2004). Adipocytokines integrate the endocrine, autocrine, and paracrine signals to mediate the multiple processes including insulin sensitivity, oxidant stress, energy metabolism, blood coagulation, and inflammatory responses which are thought to accelerate atherosclerosis, plaque rupture, and atherothrombosis (Jacobs *et al.,* 2014). This shows that the adipose tissue is not only specialized in the storage and mobilization of lipids but it is also a remarkable endocrine organ releasing the numerous cytokines.

2.5. Hypertension

Hypertension is frequently common among patients with diabetes (Matheus *et al.,* 2017).The coexistence of these two conditions increase the risk of developing macrovascular complications and also microvascular complications and close monitoring and treatment of hypertension may reduce the progression of these complications(Matheus *et al.,* 2017). Hypertension affects majority of individuals with diabetes mellitus especially those with type 2 diabetes mellitus and its pathogenesis is complex, involving interactions between genetic predisposition and a range of environmental factors (Gilbert *et al.,* 2017). Hypertension commonly occurs without abnormal renal function and insulin resistance precipitate hypertension by stimulating the sympathetic nervous system and the rennin – angiotensin system, promoting sodium retention (Gilbert *et al.,* 2017)

2.6. Complications of Diabetes Mellitus

Diabetes is associated with a number of complications. These complications are wide ranging and are due at least in part to chronic elevation of blood glucose levels, which leads to damage of blood vessels (angiopathy). In diabetes, the resulting complications are grouped under microvascular disease and macrovascular disease. Microvascular complications include retinopathy, nephropathy, and neural damage or neuropathy. The major macrovascular complications include accelerated cardiovascular disease resulting in myocardial infarction and cerebrovascular disease manifesting as strokes. Other chronic complications of diabetes include depression, (Nouwen *et al.,* 2011), dementia, and sexual dysfunction (Adeniyi *et al.,* 2011).

2.6.1. Diabetic Nephropathy

Diabetes is one of the leading causes of end-stage renal failure. The pathophysiologic event that takes place in diabetic nephropathy is damage to the basement membrane with associated renal damage. There is a progressive thickening of the basement membrane and damage to mesangial and vascular cells leading to the passage of macromolecules which may activate inflammatory pathways that contribute to secondary damage (Evans & Capell, 2010). Activation of the transforming growth factor-β (TGF-β) system is also said to be linked in the pathogenesis of diabetic nephropathy, based on the properties of TGF-β, as well as the observation that levels of TGF-β mRNA and protein are significantly increased in the glomeruli and tubulointerstitium in human diabetes and in animal models (Wendt *et al.,* 2013). Some of the risk factors for the development of diabetic nephropathy include hypertension, hyperglycaemia smoking and high protein diet. Treatment intervention may include screening for the earliest stages of renal damage and aggressively controlling blood glucose and blood pressure which can help prevent further renal damage (Evans and Capell, 2010; Ayodele *et al.,* 2014).

2.6.2. Diabetic Neuropathy

The most common complication forms of diabetic neuropathy are autonomic neuropathy and distal symmetrical polyneuropathy (DSPN) with DSPN being the most common manifestation, but many patterns of nerve injury can also occur (Jimenez-Cohl *et al.,* 2016). The risk factor is hyperglycaemia. Sensorimotor neuropathy is associated with pain, sensory loss and paresthesia. Gastroparesis and Genitourinary dysfunctions are the main complications of diabetic neuropathy. The pathology involves oxidative stress, advanced glycation end products, polyol pathway flux and protein kinase C activation which contribute to nerve dysfunction and microvascular disease (Duby *et al.,* 2014). In addition to motor neuron dysfunction, the autonomic nervous system is also influenced by diabetes. One common abnormality in autonomic function seen in individuals with diabetes is orthostatic hypotension, due to an inability to adjust heart rate and vascular tone to maintain blood flow to the brain. The autonomic nerves innervating the gastrointestinal tract are also affected leading to gastroparesis, nausea, bloating, and diarrhoea, which can also alter the efficacy of oral medications. In particular, delayed gastric emptying can dramatically affect glycaemia control by delaying the absorption of key nutrients, as well as antidiabetic agents leading to imbalances in glucose homeostasis. The wide variety of clinical manifestations seen with neuropathy, in addition to impaired wound healing, erectile dysfunction, and cardiovascular disease, can severely impede quality of life. Indeed, autonomic markers can predict which diabetic individuals have the poorest prognosis following myocardial infarction (Barthel *et al.,* 2016). Consistent with other complications, the duration of

diabetes and lack of glycaemia control are the major risk factors for neuropathy in both major forms of diabetes (Forbes & Cooper, 2017). Other than optimization of glycaemia control and management of neuropathic pain, there are no major therapies approved in either Europe or the United States for the treatment of diabetic neuropathy. In addition, as is seen with other complications, the mechanisms leading to diabetic neuropathy are poorly understood. At present, treatment generally focuses on alleviation of pain, but the process is generally progressive.

2.6.3. Diabetic Retinopathy

Diabetic retinopathy develops over many years, and almost all patients with type 1 diabetes (Hirai *et al.,* 2016) and most having type 2 diabetes, exhibit some retinal lesions after 20 years of disease. Furthermore, whereas in type 1 diabetes the major vision threatening retinal disorder appears to be proliferative retinopathy (Klein *et al.,* 2014), in type 2 diabetes there is a higher incidence of macula oedema. Nevertheless, only a minority of such patients will have progression resulting in impaired vision. In addition to maintenance of blood pressure and glycaemia control, there are a number of treatments for diabetic retinopathy that have efficacy in reducing vision loss. These three treatments include laser photocoagulation, injection of the steroid triamcinolone, and more recently vascular endothelial growth factor (VEGF) antagonists into the eye, and vitrectomy, to remove the vitreous. However, there is no agreed medical approach to slow disease progression before the use of these rather invasive treatments.

2.6.4. Cardiovascular Disease

There is increased risk of cardiovascular disease (CVD) in diabetes, such that an individual with diabetes has a risk of myocardial infarction equivalent to that of non-diabetic individuals who have previously had a myocardial infarction (Haffner *et al.,* 2010). CVD accounts for more than half of the mortality seen in the diabetic population (Haffner *et al.,* 2010) and diabetes equates to an approximately threefold increased risk of myocardial infarction compared with the general population. Atherosclerosis is a complex process involving numerous cell types and important cell-to-cell interactions that ultimately lead to progression from the "fatty streak" to formation of more complex atherosclerotic plaques. These complex atherosclerotic plaques may then destabilize and rupture, resulting in myocardial infarction, unstable angina, or strokes. The precise mechanism is unknown. However, dysfunction within the endothelium is thought to be an important early contributor. The endothelium is crucial for maintenance of vascular homeostasis, ensuring that a balance remains between vasoactive factors controlling its permeability, adhesiveness, and integrity such as Angiotensin II (ANG II) and nitric oxide, but this balance appears compromised by diabetes (Okon, 2015). Localized abnormalities drive atherogenesis, where immune cells including macrophages and T cells can bind to the vessel wall. This initiates movement of low-density lipoprotein into the subendothelial space leading to foam cell and fatty streak formation (Glass, 2017) which are commonly seen at sites of turbulent flow such as bifurcations, branches, and curves (Glass, 2017). Ultimately, proliferation of smooth muscle cells and matrix deposition, often with associated necrosis, result in the formation of a complex atherosclerotic plaque, which may occlude the blood vessel at the site of formation such as in the coronary or femoral circulation or become an embolus occluding blood vessels at distant sites, commonly originating from within carotid vessels and reaching the cerebral circulation.

2.6.5. Erectile Dysfunction

Erectile dysfunction (ED) affects approximately 34 % to 45 % of men with diabetes and has a negative impact on quality of life (Eardley *et al.,* 2014). Studies have shown that alteration of the cyclic guanosine monophosphate (cGMP /nitric acid (NO) pathway among men with diabetes with impaired vascular relaxation is related to endothelial dysfunction (Angulo *et. al.,* 2014). Among individuals with diabetes, the risk factors that may lead to ED include increasing age, poor glycaemic control, hypertension, cigarette smoking dyslipidemia, androgen deficiency states and cardiovascular disease (CVD) (Brock & Harper, 2017).

2.7. Management of Diabetes Mellitus

2.7.1. Insulin

Insulin is lifesaving pharmacological therapy for people with type 1 diabetes. This hormone is primarily produced by recombinant DNA technology and is formulated either as structurally identical to human insulin or as insulin analogues (McGibbon *et al.,* 2017). Insulin regimens should be tailored to the individual's treatment goals, lifestyle, diet, age, general health, motivation, hypoglycaemia awareness status and ability for self-management. Social and financial aspects also should be considered. While fixed-dose regimens once were common and still may be used in some circumstances, they are not encouraged. The intensive insulin treatment of type 1 diabetes significantly delays the onset and slows the

progression of microvascular and macrovascular complications (McGibbon *et al.,* 2017). The most successful protocols for type 1 diabetes rely on basal-bolus regimens that are used as a component of intensive diabetes therapy. Basal insulin is provided by intermediate-acting insulin or a long-acting insulin analogue once or twice daily. Bolus insulin is provided by short-acting insulin or a rapid-acting insulin analogue given at each meal. Such protocols attempt to duplicate normal pancreatic insulin secretion. Prandial insulin dose must take into account the carbohydrate content and glycaemia index of the carbohydrate consumed, exercise around meal time. Regular insulin should ideally be administered 30 to 45 minutes prior to a meal. However, it has been known that pre-prandial injections achieve better postprandial control and, possibly, better overall glycaemia control (G McGibbon *et al.,* 2017). Complications of insulin therapy include weight gain and hypoglycaemia. Hypoglycaemia may result from an inappropriately large dose, from mismatch between the peak delivery of insulin and food intake.

2.7.2. Oral hypoglycemic agents

2.7.2.1. Sulfonylureas

The first generation of sulfonylureas includes tolbutamide, acetohexamide, tolazamide, and chlorpropamide. A second generation of sulfonylureas has emerged and includes glibenclamide, glipizide, gliclazide, and glimepiride. They are more potent than the first generation agents. Sulfonylureas act by stimulating insulin release from pancreatic ß-cells by binding to sulfonylurea receptors (SUR) on the ß-cell plasma membrane, causing closure of adenosine triphosphate (ATP) sensitive potassium channels, leading to depolarization of the cell membrane. This in turn opens voltage-gated channels, allowing influx of calcium ions and subsequent secretion of preformed insulin granules (Bastaki, 2013).

2.7.2.2. Metformin

Metformin has a very low rate of causing lactic acidosis. When given alone or in combination with a sulfonylurea improves glycaemia control and lipid concentrations in patients who respond poorly to diet or to a sulfonylurea alone. Studies have shown that metformin improves insulin resistance in the liver, skeletal muscle, and adipose tissue, a major pathogenic component of type 2 diabetes (Bailey, 2014). The mechanism of action of metformin is not fully understood. It has been shown to increase peripheral uptake of glucose and to reduce hepatic glucose output by approximately 20-30% when given orally. Metformin has also been shown to decrease serum triglycerides and fatty acid concentrations and slows the rate of lipid oxidation, actions that indirectly inhibit gluconeogenesis (Wu *et al.,* 2015).

2.7.2.3. Thiazolidinediones

Thiazolidinediones (TZDs) are chemically and functionally unrelated to the other classes of oral antidiabetic agents. Two compounds in this class are currently in use. Rosiglitazone (Avandia) and pioglitazone (Actos) are the two thiazolidinediones in use. Thiazolidinediones are found in key target tissues for insulin action such as adipose tissue, skeletal muscle and liver. They exert their principal action by lowering insulin resistance in peripheral tissue, and also by lowering glucose production by the liver1 (Park et al., 2010).Thiazolidinediones increase glucose transport into muscle and adipose tissue by enhancing the synthesis and translocation of specific forms of the glucose transporter proteins.

2.7.2.4. Meglitinide analogues

The meglitinide analogues are a new class of drugs developed to improve early-phase insulin secretion, which is one of the earliest pathophysiolocal manifestations of type 2 DM. These are derived from the meglitinide portion of sulfonylureas. The meglitinide analogues act on ß-cell receptors to stimulate insulin secretion by binding to the sulfonylurea receptor subunit and closing the K+ ATP channel. Probably at a site distinct from that of the sulfonylurea receptor Closure of the potassium channel leads to depolarization of ß-cell plasma membrane, which promotes influx of calcium ions through voltage-gated calcium channels, resulting in exocytosis of insulin granules (Bastaki et *al.,* 2013).

2.8. Anti Diabetic Medicinal Plants

2.8.1. Cabbage

Cabbage is one of the most important crop plants of the species *(Brassica oleracea)*. It is a herbaceous, biennial, dicotyledonous flowering plant with leaves forming a characteristic compact head. The cabbage is differentiated into white head cabbage *(Brassica oleraceavar capitatasub. varalba)* and red head cabbage *(Brassica oleraceavar. capitata sub. var. rubra)*. It is widely consumed probably due to the its acceptable price, consumer preferences and availability at local markets The influence of cabbage consumption on human health is evident and is, in addition to being a source of vitamins and fibre, connected with secondary metabolites called glucosinolates, which are known to possess anticarcinogenic properties (Sarikamiş *et al.,* 2015). Cabbage is rich in phytochemicals such as polyphenolics, glucosinolates, carotenoids and vitamin C that have showed antioxidant, anticancer (Podsędek, 2014) and potential anti-obesity properties

(Williams *et al.,* 2019). Raw cabbage juice can potentially heal an ulcer within 14 days of treatment. It is believed that the high level of glutamine is responsible for this healing effect. The ulcer healing properties of cabbage juice was verified in the 1950s in clinical trials both in United States and Europe (Priya, 2017). It has also been known that taking the combination of cabbage and Broccoli juice daily for 12 weeks significantly reduce the blood levels of low – density lipoproteins (Takai *et al.,* 2013). Epidemiological studies have shown cabbage to reduce the risk of lung, stomach, colorectal, breast, bladder and prostate cancer. It is postulated that this ability comes from glucosinolate proficiency for inhibiting cell division and inducing apoptosis (Priya, 2017). Cabbage has high level of anti – oxidants, such as vitamin C which has an immune boosting effect (Singh *et al*., 2006). Cabbage extract intake reduce serum cholesterol level and enhance faecal bile acid excretion and cholesterol 7 alpha hydroxylase activity, the rate limiting enzyme for bile acid biosynthesis in the microsomal fraction liver (Priya, 2017).

2.8.2. Brassica juncea (Brassicaceae)

The aqueous extract of Brassica juncea seeds in diabetic rats at a dose of 250, 350 and 450 mg/kg p.o. significantly reduced the blood glucose level. Further its showed insulinomimetic activity in the tested group signifying its anti-diabetic effect (Thirumalai *et al.,* 2017).

2.8.3. Azadirachta indica (Neem)

Hydroalcoholic extracts of this plant showed antihyperglycaemic activity in streptozotocin treated rats and this effect is because of increase in glucose uptake and glycogen deposition in isolated rat hemidiaphragm. Apart from having anti-diabetic activity, this plant also has anti-bacterial, antimalarial, antifertility, hepatoprotective and antioxidant effects (Dheer & Bhatnagar, 2016).

2.8.4. Zea mays (Corn Silk, Indian corn)

Cornsilk is a proven diuretic. It is plentiful, cheap, and commonly used to treat cystitis, pyelitis, oliguria, and edema. It possesses hypoglycemic, antimicrobial, cholinergic and hypotensive properties. Cornsilk has more or less confirmed oral hypoglycemic activity. In one study the herb produced a constant hypoglycemic effect in starving rabbits. The active principle is not known (Amreen *et al.,* 2017).

2.8.5. Allium sativum (garlic)

This is a perennial herb cultivated throughout India. Allicin, a sulfur-containing compound is responsible for its pungent odour and it has been shown to have significant hypoglycemic activity. This effect is thought to be due to increased hepatic metabolism, increased insulin release from pancreatic beta cells and/or insulin sparing effect. Aqueous homogenate of garlic (10 ml/kg/d) administered orally to sucrose fed rabbits (10 g/kg/d in water for two months) significantly increased hepatic glycogen and free amino acid content, decreased fasting blood glucose, and triglyceride levels in serum in comparison to sucrose controls. S-allyl cystein sulfoxide (SACS), the precursor of allicin and garlic oil, is a sulfur containing amino acid, which controlled lipid peroxidation better than glibenclamide and insulin (Ravikumar *et al.,* 2017).

2.8.6. Vernonia amygdalina (Bitter-tea vernonia)

The anti-diabetic activity of the various combinations of metformin (50 mg/kg) and aqueous extracts of the leaves of *Vernonia amygdalina* (Asteraceae) (100 mg/kg) in diabetic rats were investigated. Extract and metformin at the ratios of 1:1 and 2:1 were given to both normoglycemic and diabetic. From the data it was found that, blood glucose level was decreased more significantly by the drug combination compared to the single treatment of drug in the diabetic rats (Amreen *et al.,* 2017).

2.8.7. Sphenostylis stenocarpa (Africa yam bean, Wild yam bean)

The methanolic extract of seeds of Sphenostylis stenocarpa (Leguminoseae) in diabetic rats at doses of 200, 400 and 600 mg/kg, p.o., significantly reduces the blood glucose level. Moreover, 600 mg/kg, p.o. was found to be more significant compared to other tested dose level (Okokon *et al.,* 2016).

2.8.8. Juglans regia (walnut)

Anti-diabetic effects of methanolic extract of *Juglans regia* (*J. regia*) (*Juglandaceae*) leaves was estimated in diabetic male wistar rats at 250 mg/kg, p.o. for three weeks. J.ragia significantly decreases the blood glucose, TG and total cholesterol (TC) level. Further it increased gluthione peroxidise (GPX), super oxide dismuthase (SOD) and cell antibody level significantly and therefore signified its anti-diabetic potential (Teimoori *et al.,* 2018).

3. MATERIALS AND METHODS

3.1. Materials

This chapter describes the equipment, apparatus, reagents, methods and procedures employed in this study. It entails the processes in which various data were generated.

3.1.1. Chemicals

All chemicals and drugs used (Alloxan monohydrate, chloroform, ethanol, formalin, Glibenclamide and alloxan were purchased from Drug market in Onitsha main market.

3.1.2. Equipment

Materials used were digital glucometer for blood glucose determination (Accu-check advantage, Roche Diagnostic, Company), weighing balance (GF 2000), dissecting set, syringes and needle.

3.1.3. Plant Material

Fresh cabbages were purchase in February 2022 from a local farmer at Eke-Awka market, Anambra State. Authentication and identification was done by the Taxonomist in the Herbarium section of Department of Biological sciences, Nnamdi Azikiwe University, Awka.

3.1.4. Animals

A total of fourty two male Wistar rats weighing 130-170g was used for this study. The animals was obtained from the Animal house of Department of Human Physiology, Nnamdi Azikiwe University, Nnewi. They were randomized into experimental and control groups and were kept in polypropylene cages. Standard animal feed made of pellets from grower's mash were provided to the animals. The rats were allowed access to drinking water *ad libitum* throughout the period of the study.

3.2. Methods

3.2.1. Preparation of cabbage extract

Fresh leaves of cabbage were shed, dried, grounded, and used to prepare an extract

3.2.2. Experimental induction of diabetes mellitus

Diabetes were induced by single intraperitoneal injection of alloxan monohydrate (Sigma St. Louis, M.S., U.S.A.) at a dose of 150 mg/kg body weight dissolved in 0.9% cold normal saline solution. The rats was fasted for 16 - 18h before induction (Katsumata *et al*., 1999). Since alloxan is capable of producing fatal hypoglycaemia as a result of massive pancreatic insulin release, rats were treated with 20% glucose solution orally for 6 hrs after induction. The rats were then be kept for the next 24 hrs on 5% glucose solution bottles in their cages to prevent hypoglycaemia (Dhandapani *et al*., 2002). After 72 hrs of alloxan treatment, venous blood were collected from the tail of the rats. Rats having fasting blood glucose level greater than 200 mg/dl were considered to be diabetic.

3.2.3. Experimental design

The study was carried out on alloxan induced Wistar rats. The animals were fasted for 16-18 hrs with free access to water prior to the induction of diabetes. After induction, the animals were randomly divided into 6 groups as follows:

Group 1: (positive control): Normal rats received only feed and distilled water for three weeks.

Group 2:(Negative control): Diabetic rats which received only feed and water.

Group 3: In this group**,** diabetic rats were induced with 150mg/kg of alloxan and treated with low dose of extract (cabbage extract - 150mg/kg) for 3 weeks

Group 4: In this group, diabetic rats were induced with 150mg/kg of alloxan and treated with medium dose of extract (cabbage extract- 300mg/kg) for 3 weeks

Group 5: In this group, diabetic rats were induced with 150mg/kg of alloxan and treated with high dose of extract (cabbage extract - 600mgkg).

Group 6: In this group, normal rats received high dose of extract (cabbage extract - 600mg/kg) for two weeks before it was indused diabetes 150mg/kg.

3.2.4. Determination of blood glucose levels

All venous blood samples were collected from the tail of the rats at weekly intervals for 3 weeks respectively. Fasting blood glucose levels were determined by using glucose oxidase method (Beach and Turner, 1958) using a digital glucometer (Accu-Chek Advantage, Roche Diagnostic, Germany). The results were expressed in mg/dl (Rheney and Kirk, 2000).

3.2.5. Determination of liver enzyme assay

Blood sample will be collected via cardiac puncture, which will be centrifuged to get serum for liver enzymes assay. These include: Alkaline phosphatase, Alanine aminotranferase and Aspartate aminotranferase using Reitman and Frankel method (1957).

3.2.5.1. Determination of serum aspartate aminotransferase (AST)

Aspartate aminotransferase will be estimated by the method described by Bergmeyer and Walefeld (1978). 100 µL of the reagent was added to 100 µL of the samples and then mixed and incubated at 37ºC for 1 minute. The change in absorbance of the sample will be measured per minute spectrophotometrically at the wavelength of 590 nm as follows:

$$\text{AST activity (U/L)} = \Delta AB/\text{min} \times 1768$$

3.2.5.2. Determination of serum alanine aminotransferase(ALT)

This will be estimated by the method described by Bergmeyer and Walefeld (1978). 1000µL of the reagent will be added to 100 µL of the samples and then mixed and incubated at 37ºC for 1 minute. The change in absorbance of the sample will be measured per minute spectrophotometrically at the wavelength of 590 nm as follows:

$$\text{AST activity (U/L)} = \Delta AB/\text{min} \times 1768$$

3.2.5.3. Determination of serum alkaline phosphatase (ALP)

Alkaline phosphatase will be estimated by the method described by, Bowers and Mc Comb (1966). 0.5 ml of the reagent will be added to 0.05 ml (50 µL) of the sample and then mixed and incubated at 37ºC for 10 minutes. The change in absorbance of the sample will be measured per minute spectrophotometrically at the wavelength of 590 nm as follows:

Absorbance of sample / Absorbance standard × Value of standard (U/L).

3.3. Statistical Analysis

All data will be will be expressed as mean ± SEM. The data obtained will be statistically analyzed using analysis of variance (ANOVA) with *Tukey's* multiple comparison post hoc tests to compare the level of significance between control and experimental groups. All statistical analysis will be evaluated using SPSS version 20.0 software. The values of $P < 0.05$ were considered as significant.

4. RESULT

TABLE 4.1 Figure 4.1 Comparison of the Initial and final weight of each of the group.

EXPERIMENTAL GROUPS	FINAL BODY WEIGHT (g) Mean±SEM	INITIAL BODY WEIGHT (g) Mean±SEM	WEIGHT DIFFERENCE	T-VALUE	P-VALUE
GROUP A	193.05±6.85	160.50±4.50	32.55	2.87	0.21
GROUP B	104.10±7.92	146.70±4.54	-42.60	-6.17	0.01*
GROUP C	159.03±26.94	142.53±3.82	16.50	0.58	0.62
GROUP D	133.20±17.90	143.90±0.40	-10.70	-0.59	0.66
GROUP E	160.15±1.05	143.85±8.13	16.30	3.47	0.18
GROUP F	190.77±7.52	225.43±6.84	-64.66	-8.55	0.01*

* Significant at $P \leq 0.05$

Data were analyzed using ANOVA and values were considered significant at P<0.05.

There was significant decrease in the mean animal body weight of the groups B and F when initial body weight was compared to final body weight.

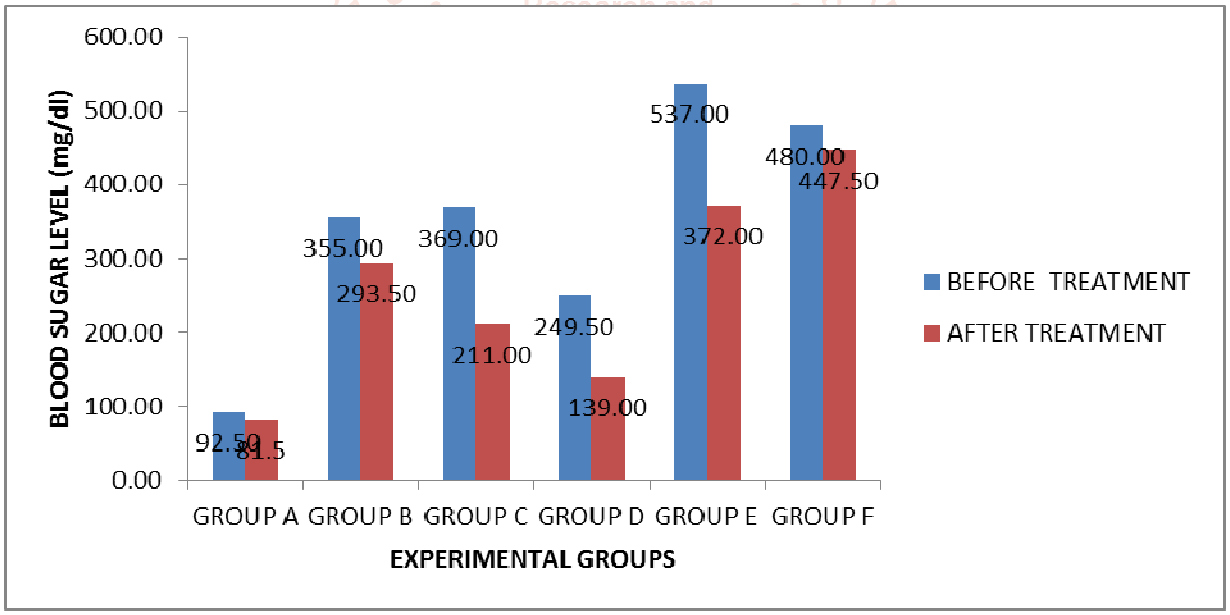

FIGURE 4.1: Comparison of the effect of the treatment on the blood glucose level before and after treatment with cabbage extract.

Data were analyzed using students T test and data were considered significant at P≤0.05 and P>0.05 means not significant.

There was significant no significant decrease in the blood glucose levels in all the groups when the blood sugar level on diabetic where compared to the blood sugar levels after treatment with cabbage extract.

Table 4.2: Comparison of the effect of the treatment on ALP, AST and ALT of the animals between the test groups and the control group.

Experimental Groups	ALP(U/L) Mean±SEM	F-Value	P-Value	ALT(U/L) Mean±SEM	F-Value	P-Value	AST Mean±SEM	F-Value	P-Value
GROUP A	34.00±1.00			15.44±0.19			13.46±1.50		
GROUP B	55.00±15.00		0.15	15.81±0.02		0.82	13.74±0.22		0.79
GROUP C	69.50±4.50	3.17	0.03*	17.61±1.31	1.21	0.21	14.49±0.13	1.31	0.35
GROUP D	60.50±12.50		0.08	15.12±1.27		0.84	14.28±0.15		0.45
GROUP E	78.50±2.50		0.01*	14.59±0.24		0.60	14.02±1.01		0.67
GROUP F	72.50±8.50		0.02*	17.25±1.94		0.29	15.81±0.14		0.06

*Significant at P≤0.05

Data were analyzed using One-way ANOVA followed by Post HOC Fisher's LSD multiple comparison, and data were considered significant at P≤0.05 and P>0.05 means not significant.

There was significant increase in the ALP levels of groups C, E and F when compared to group A.

There was no significant difference in the AST and ALT levels of all the test groups when compared to the control group.

Table 4.3: Comparison of the effect of the treatment on ALP, AST and ALT of the animals between the test groups and group B.

	ALP(U/L) Mean±SEM	F-Value	P-Value	ALT(U/L) Mean±SEM	F-Value	P-Value	AST Mean±SEM	F-Value	P-Value
GROUP B	55.00±15.00			15.81±0.02			13.74±0.22		
GROUP C	69.50±4.50		0.30	17.61±1.31		0.29	14.49±0.13		0.49
GROUP D	60.50±12.50	3.17	0.68	15.12±1.27	1.21	0.67	14.28±0.15	1.31	0.62
GROUP E	78.50±2.50		0.11	14.59±0.24		0.46	14.02±1.01		0.80
GROUP F	72.50±8.50		0.22	17.25±1.94		0.39	15.81±0.14		0.09

*Significant at P≤0.05

Data were analyzed using One-way ANOVA followed by Post HOC Fisher's LSD multiple comparison, and data were considered significant at P≤0.05 and P>0.05 means not significant.

There was no significant difference in the ALP, AST and ALT levels of all the test groups when compared to the group B.

5. Discussion and Conclusion

5.1. Discussion

Diabetes is a disease that is characterized by abnormalities in carbohydrate, protein, and lipid metabolism, causing a great challenge to healthcare professionals who care for people with diabetes (Cheng, 2013). Previous studies have observed that vegetables play a protective role against the development of human diseases. (Baboota et al., 2013, Magrone et al., 2013, Liu, 2013, Scicchitano et al., 2014). In the present study there was decrease in blood levels in each experimental group, this observed decrease in serum levels of blood glucose when the blood glucose levels after diabetics induction were compared to blood sugar levels after treatment with cabbage extract demonstrated the hypoglycaemic effect of cabbage extract. Muhammad et al., (2016) also reported hypoglycaemic effect of cabbage supplement. These results agree with the work of Gaafar et al, (2014), who demonstrated the hypoglycaemic effect of both extract of white and red cabbages in STZ induced type-2 diabetes in rats. The decrease may be due to the effect of different polyphenolic compound present in cabbage (Muhammad et al., 2016). These compounds, for example flavonoids and other alkaloids have been reported to have anti-diabetic properties. The finding of this study is also in agreement with that of Alsuhaibani, (2013) who reported the hypoglycaemic and hypolipidaemic activities of red cabbage and manganese for the treatment of diabetes in rats. It was also reported that the administration of anthocyanins (also found in cabbage) markedly decreased glucose levels and increase utilization of glucose by tissues in diabetic rats (Nizamutdinova et al., 2009).

The liver enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) are considered as biomarkers of liver toxicity and are used in the evaluation of hepatic disorders (Oh and Hustead, 2011). The result of the current study indicated significant increase in the ALP levels of groups that was treated with 150mg/kg,

600mg/kg cabbage extract respectively, when compared to the control group, the group that was given 600mg/kg before induction of diabetics also showed significant increase in ALP when compared to control. It was also observed that there was no significant difference in the AST and ALT levels of all the test groups when compared to the control group. These findings are not in agreement with the findings of Muhammad et al., (2016), who observed significant increase in serum levels of ALT and AST in diabetic rats treated with cabbage supplement when compared with the control. The current study observed significant increase in the ALP levels of the groups treated with low and high dose of cabbage extract when compared to control group, while Muhammad et al, (2014) reported significant decrease in ALP when compared to control. The results of the present study is not in accordance with the work of (Gaafar et al., 2014), who reported a significant increase in serum level of ALT and AST in diabetic rats treated with extract of both white and red cabbages in comparison with the control. The finding of the current study is in agreement with (Gaafar et al., 2014) who also observed significant increase in serum ALP levels when compared to the control group. The findings of this study also disagree with the work of (Alsuhaibani, 2013; Maha and El-Motaleb,2012), they observed a significant decrease in serum liver enzymes (ALT, AST and ALP) in diabetic rats who were treated with red cabbage powder and red cabbage extract. The increase in the activities of these serum enzymes may be due to the fact that cabbage when eaten in excess can be goitrogenic, and in goitrogenic conditions, liver enzymes activities are increased (Oh and Hustead, 2011). This may explain the marked increase in the liver ALP as observed in the present study.

There was no significant difference in the ALP, AST and ALT levels of all the test groups when compared to the diabetic group without treatment as shown in table 4.3. The current study also observed no significant difference in these enzymes levels when the diabetic untreated group was compared to the control group this is an indication that cabbage extract has an effect that lead to increase ALP as observed in the study.

5.2. Conclusion

The results obtained from the study demonstrated that cabbage extracts reduced the high blood sugar levels as observed in diabetic rats in the present. The present study indicated a marked increase in the ALP levels which is suggesting an adverse effect of cabbage on the liver, therefore there is the need for more study on the toxicological profile of cabbage on the liver.

RECOMMENDATION

More study should be carried out to investigate the effect of long term administration of cabbage extract on the liver.

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