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Original Research Article

Ethanolic Extract of *Ficus vogelii* Ameliorates Dyslipidemia in Diabetic Albino Wistar Rats

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Abstract	Keywords
Ficus vogelii (FV) is used in Nigeria as an effective anti-diabetic, anti-anorexia and as an anti-anemia herb to boost the hemoglobin level in children and increase their body weights. The plant is also used for the treatment of diabetes and cardiovascular diseases in adult populations, including high blood pressure. The aim of this study is to evaluate the hypolipidemic and hypocholesterolemic effect of ethanolic extract of Ficus vogelii (FV) leaves in experimental animal models after 21 days of administration. The LD ₅₀ of FV was determined by the Lorke method. Twenty (20) Albino Wistar rats of both sexes weighing between 150-180g were divided into 4 groups of five (8) animals each. Groups 2, 3 and 4 were made diabetic by a single dose intraperitoneal injection of streptozotocin (45mg/kg b.w) dissolved in 0.1M pH 4.50 (sodum citrate) buffer via a syringe. Group 1 served as normal control (NC) and was given 0.2ml of 10% dimethyl sulphoxide (DMSO). Group 2 served as diabetic control (DC) and was not treated. Group 3 was treated with 400mg/kgbw of Metformin (METF) and group 4 was treated with 400mg/kg bw of FV extract. Total cholesterol concentration decreased significantly (p<0.05) in FV treated group (122.80±20.41mg/dL) and Metformin (121.45±15.77mg/dL), when compared to the DC (139.18±27.67 mg/dL). Triglyceride concentration decreased significantly (p<0.05) in FV (136.82±10.46 mg/dL) and METF (134.35±17.92 mg/dL) which compared well with NC (132.92±14.17mg/dL), and was significantly (p<0.05) different from DC (151.61±4.83mg/dL). FV significantly (p<0.05) increased HDL-C (20.40±2.48 mg/dL) when compared to standard DC group (16.05±1.02 mg/dL), and the NC group (39.98±7.27 mg/dL). FV extract and METF did not significantly (p>0.05) affect levels of LDL-C. The concentration of LDL-C in FV group (55.46±16.85 mg/dL) compared well with the value of METF (63.42±30.16 mg/dL) and was significantly different from value of NC (25.10±11.89 mg/dL). VLDL-C of FV group (26.59±2.83 mg/dL), and METF (27.36±2.09 mg/dL). Compar	Cardiovascular diseases Ficus vogelii Hypocholesterolemia Hypolipidemia Metformin

Introduction

Hyperlipidemia is the most common form of dyslipidemia involving abnormally elevated levels of all lipids and lipoproteins in the body (WHO, 2002; Sauders, 2007). It could be caused by genetic abnormalities in the case of primary hyperlipidemia subtype or arise as a result of underlying causes such as diabetes in the case of secondary hyperlipidemia subtype (Ahren et al., 1999; Sauders, 2007).

There are several reports associating lipid abnormalities and dyslipidemia with diabetes (National Diabetes Statistics Report, 2014). Particularly, it was reported that type 2 diabetes (non insulin dependent), presents with elevated levels of total cholesterol, very low density lipoprotein (VLDL), triglyceride concentration and lowering of high density lipoprotein (HDL) cholesterol, as well as increased concentration of low density lipoprotein (LDL) cholesterol. It is also marked by high levels of blood glucose sugar, resulting from defects in insulin production, insulin action or both (National Diabetes Statistics Report, 2014).

The number of people with diabetes is increasing due to population growth, aging, urbanization, changing lifestyles and increasing prevalence of obesity and physical inactivity (Betterle et al., 1983). It has been suggested that Nigeria, whose population subsists mainly on carbohydrate-based food with little or no physical activity, may record higher incidence of obesity and diabetes by 5% by 2020 (Igile et al., 2015, unpublished). Diabetes is regarded as a modifiable risk factor for cardiovascular disease due to its influence on atherosclerosis and high blood pressure. Type 1 diabetes has variously been associated with dyslipidemia, and this type of diabetes has also been shown to present lipid abnormalities in experimental animal models (Akan, 2006; Ebong et al., 2006; Atangwho et al., 2007; Efiong et al., 2013; Iwara et al., 2015). Lipid abnormalities itself has been associated with high blood pressure, atherosclerosis and other cardiovascular diseases. Kidney dysfunction and elevated intracellular sodium electrolyte are some of the other conditions in diabetes which like lipid abnormalities, complicate the management of the disease (Odey et al., 2014; Igile et al., 2015, in press)

Obesity, overweight and cardiovascular diseases (CVDs) are considered some of the topmost causes of deaths globally (WHO, 2014; Smith et al., 2014). This is

because more people die annually from obesity and diabetes-related cardiovascular diseases than from any other cause. An estimated 17.3 million people died from cardiovascular disease in 2008, representing 30% of all global deaths (WHO, 2014; Goff et al., 2014). WHO also reported that most of these deaths are traceable to obesity and diabetes-related complications, including liver and kidney diseases (WHO, 2014).

Plasma cholesterol is transported via lipoproteins and categorized into four classes based on cholesterollipoprotein complex (Steinberg, 2005). They include the very low density lipoprotein (VIDL), the intermediate density lipoprotein (IDL), low density lipoprotein (LDL), and high density lipoprotein (HDL). Research shows that cholesterol transport in the various lipoproteins is a factor for the occurrence of cardiovascular diseases. For example, HDL particles unlike the larger particles transfer fat away from cells, artery walls and tissues through the bloodstream back to the liver (Steinberg, 2005). On the other hand, LDL particles deliver fat molecules to macrophages in the wall of arteries, thus potentially increasing the rate of occurrence of cardiovascular diseases. In adults LDL is strongly associated with a higher risk and HDL is associated with a lower risk of coronary heart disease (Steinberg, 2006).

Lowering plasma lipids concentration through dietary and pharmacological therapy has been shown to decrease the incidence of atherosclerotic events and other cardiovascular diseases (Steinberg, 2005). It has been shown that, management or treatment of hyperlipidemia with statins and fibrates may cause a marked increased side effect such as myositis, joint pain and liver and kidney damage (Lewis, 2006). Therefore, traditional therapies and ethnopharmacological options are being explored, developed and applied by many cultures the world over in the management of several metabolic and endocrine diseases, including diabetes and cardiovascular disease and their complications. Ethno-medical option is explored owing to the fact that plants are organic and safer, with minimal or no adverse effect and their use is cost effective for the poor (Ebong et al., 2008).

Ficus vogelii is a member of the fig genus. It is found mostly in the Guinea savannah vegetation belt of West and Central Africa. In the middle belt of Nigeria, it cooccurs with its sister specie (Ficus asperifolia). The two species are closely look-alike except by small

differences in leaf venation. In Obudu culture, the specie is called "kujung" and it is used as a green-leafy vegetable in various local dishes. Extract of the leaf is used locally for the treatment of anemia, diabetes, wounds and malaria. Extract of the leaf is also used for the treatment of stomach ulcers and as a local antimicrobial agent. The leaf is also reported by ethnomedical practitioners as having high efficacy in ameliorating hemogglobinopathies, probably the reason why it is used to boost immunity in HIV patients (Bamikole et al., 2004). The leaf extract of other species has been reported to have strong anti-inflammatory effect (Recio, 1995) and anti-malarial properties (Gbeassor et al., 1990).

Therefore, this study aimed at evaluating the hypolipidemic and hypocholesterolemic effect of methanolic crude extract of *Ficus vogelii* in streptozocin-induced diabetic Albino Wistar rats, to confirm ethno-medical claim of the use of the plant.

Materials and methods

Collection of plant

Fresh leaves of *Ficus vogelii* were harvested from a farm in Obudu Local Government Area of Cross River State. The plant was authenticated by a botanist in the Department of Botany, University of Calabar, Nigeria. The leaves were air dried at room temperature (25-28°C), at the Endocrine laboratory of the Department of Biochemistry, University of Calabar. The dried leaves were blended into a powdery form using a hand mill to afford 650g sample. This was stored in well labeled polyethylene bag under refrigeration until required.

Chemicals and reagents

All chemicals and reagents used in this study were obtained commercially and were all of analytical grade. Lipid cholesterol components (VLVL, LDL, HDL, TG and TC) were assayed by standard analytical methods using Agappe Assay kits (Germany).

Preparation of plant extract

Five hundred (500g) of the powdered leaves were soaked for 48hrs in 80% ethanol. The mixture was then filtered first with cheese cloth and then re-filtered with Whatmann No 1 filter paper to obtain a homogenous clear filtrate. The filtrate was concentrated *in vacuo*,

using a rotary evaporator at <40°C to yield a sticky paste (2.84g). This was stored under refrigeration at <4°C until required.

Phytochemical analysis

0.6g of the extract was used for quantitative phytochemical analysis. Tannins, phenolics, total polyphenols, flavonoids, saponins, triterpenoids, carotenoids, sesquiterpene lactones, and alkaloids were carried out according to known and standard methods. Tannins were estimated using the Folin-Denins spectrophometric method (Pearson, 1976). Saponin content was determined using the method of Birk et al. (1963) as modified by Hudson and El Difrawi (1979). Flavonoids, alkanloids and sequiterpene lactones were fractionated by column chromatography in order of solvent polarity. Each fraction was extracted using ethyl acetate, evaporated and quantitatively determined by gravimetry as described by Harbone (1973).

Animals and experimental design

Thirty two (32) Albino Wistar rats of both sexes, weighing between 150-189g were obtained from the animal house of the Department of Genetics and Biotechnology, University of Calabar, Nigeria. The animals were allowed to acclimatize for 7 days in the animal house of the Department of Biochemistry, in ventilated cages (25±2.0°C) under 12 h light/dark cycle. The animals were fed standard rat pellets and allowed free access to water *ad libitum* throughout the period of the experiment. The rats assigned to 4 groups of 8 animals each as shown in table 1 below.

Table 1. Animal grouping and experimental design.

Group	No. of animals	Dose of treatment
Normal control	8	0.2 ml of 10% dimethyl
(NC)		sulphoxide
Diabetic control	8	0.2 ml of 10% dimethyl
(DC)		sulphoxide
Metformin	8	400 mg/kg/body weight
(METF)		
Ficus vogelii (FV)	8	400 mg/kg/body weight

Induction of experimental diabetes

The Albino Wistar rats were subjected to 12 hours fast prior to diabetic induction. Diabetes was induced by a single dose of streptozotocin (45mg/kg body weight) dissolved in 0.1M sodium citrate buffer, pH 4.5 via

intraperitoneal injection (IP) using a 5ml hypodermic syringe and needle. Diabetes was confirmed after 3 days if blood sugar level was >250 mg/dl, estimated in blood from the tail vein of the animals using a glucometer.

Extract and drug administration

The plant extract was reconstituted in 20% dimethylsuphozide (DMSO) and administered to groups 4 animals orally, via gastric intubation at a dose of 400mg/kg body weight. Group 3 animals were given 400mg/kg body weight of standard drug (Metformin), while group 1 (NC) and group 2 (DC) animals received 0.2ml of DMSO (placebo). All animals were treated for 21 days. The body weight of the animal were monitored at 7 days interval using an electronic weighing balance and also the glucose level was checked at 7 days interval with a glucometer throughout the experimental period.

Collection of blood samples for analysis

At the end of 21 days, the rats were anaesthetized using chloroform. Rats were placed on a dissecting slab where a longitudinal cut was first made abdominally to the rib cage followed by transverse cut to the limbs. This exposed the heart of animals. Blood was collected through cardiac puncture using a sterile syringe and needle into properly labeled sterile sample bottles. Each blood sample was centrifuged at 500rpm for 5 minutes and serum obtained transferred into labeled sterile sample bottles for Biochemical analysis.

Statistical analysis

Data obtained from this study were analysed by descriptive statistics and presented as mean \pm standard error of mean (SEM) of three determinations, using the statistical software package SPSS for windows version 11.0 (SPSS Inc. Chicago IL). Differences between means were separated using the ANOVA and multiple comparison tests. Values of p<0.05 were taken as being significant.

Results

Table 2 shows the result of the quantitative phytochemical analysis of the air-dried leaf sample of *Ficus vogelii*. The results showed that the plant contained a high concentration of polyphenols, followed by saponins and flavonoids. Carotenoids also appeared at reasonable concentrations in the plant.

Table 2. Phytochemical composition of air-dried leaves of Ficus vogelii.

Parameter	Result (mg/100g)
Saponins	3.57 ± 0.24
Alkaloids	0.92 ± 0.05
Flavonoids	3.37 ± 0.05
Coumarins	2.48 ± 0.04
Steroids	2.10 ± 0.02
Triterpenoids	1.75 ±0.03
Carotenoids	2.97 ± 0.15
Polyphenols	7.49 ± 1.21
Cardiac glycocides	1.72 ±0.06
Mean \pm SEM, n = 3.	

The results of the lipid components are presented in Figs. 1-5. Fig. 1 shows the effect of *Ficus vogelii* (FV) on High density lipoprotein cholesterol (HDL-c). The *Ficus vogelii* treated group showed a significant (p>0.05) increase in HDL-c when compared with the normal control (NC).

Fig. 1: High-density lipoprotein concentrations of the different experimental groups. Values are expressed as mean \pm SEM, n+5. *Significantly different from NC at p<0.05.

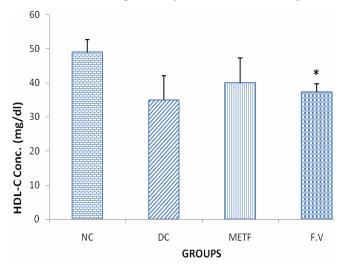


Fig. 2 shows the effect of ethanolic extract of *Ficus vogelii* (FV) on Very low density lipoprotein cholesterol (VLDL-c). *Ficus vogelii* treated group showed a significant (p<0.05) decrease in VLDL-c. On the other hand, Fig. 3 shows the effect of *Ficus vogelii* (FV) on low density lipoprotein cholesterol (LDL-c). The FV treated group showed a significant (p<0.05) decrease in LDL-c. Fig. 4 show the effect of the plant extract on the triglyceride concentration in the animal group treated with the extract, while Fig. 5 shows the effect of the plant extract on total cholesterol concentration in animals previously induced with type 1 diabetes with

streptozotocin. Animals treated with FV extract gave significantly (p<0.05) deceased concentrations of triglycerides and total cholesterol concentrations respectively.

Fig. 2: Very-low density lipoprotein concentrations of the different experimental groups. Values are expressed as mean±SEM, n=5.

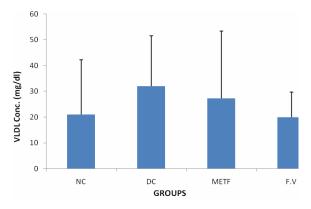


Fig. 3: Low density lipoprotein concentrations of the different experimental groups. Values are expressed as mean±SEM, n=5.

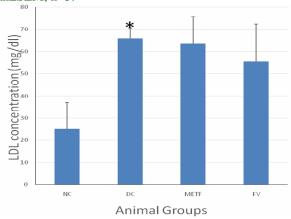


Fig. 4: Triglyceride concentrations of the different experimental groups. Values are expressed as mean \pm SEM, n+5. *Significantly different from NC at p<0.05.

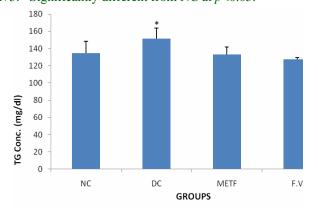
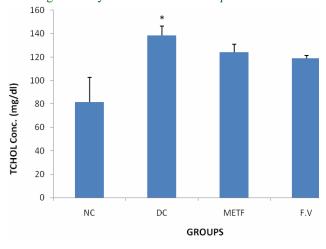


Fig. 5: Total cholesterol concentrations of the different experimental groups. Values are expressed as mean±SEM, n+5. *Significantly different from NC at *p*<0.05.



Discussion

In diabetes condition, there is usually observed high plasma lipid cholesterol concentrations, dyslipidemia and hyperglycemia. Dyslipidemia is always associated with diabetic milletus which is a risk factor for some endocrine-related diseases including cardiovascular disease. It is thought that this occurs due to deposition of plaque along artery walls caused by crystals of LDL-c, leading to blockage of arterial passage and atherosclerosis. Disproportionate perturbations are usually observed in dyslipidemia, depending on the extent of diabetic condition (Aguila and Manderim-de-Lacerda, 2003). It has been reported that cardiovascular diseases (CVDs) may be said to be the number one cause of death globally (WHO, 2014).

Human diets worldwide are rich in lipids, fats and oils which are precursor substances to LDL, VLDL, IDL and HDL-cholesterol, as well as triglycerides and total cholesterol. High concentrations of these lipoproteins, HDL-c except have been associated cardiovascular disease. In this study, there was LDL, VLDL, total cholesterol elevated and triglyceride concentration when the animals were induced with diabetes. Under this condition, HDL concentration decreased (Ahren et al., However, when the animals were treated with extract of Ficus vogelii, there was a significant decrease (p<0.05) in TC, LDL, VLDL and triglyceride concentrations, while the HDL-C concentration was elevated. The results were consistent with those of earlier studies (Ebong et al., 2006, 2008; Atangwho et al., 2007; Efiong et al., 2013; Iwara et al., 2015).

Hyperlipidemias are disorders of the rates of synthesis or clearance of lipoproteins from the bloodstream, biochemically detected by measuring plasma triacylglycerol and total cholesterol (Steinberg, 2005, 2006). In this study, diabetes induction raised plasma triacylglycerol and total cholesterol concentrations to >159mg/dl and >140mg/dl respectively. Hyperlipidemia may be classified on the basis of which class of lipoprotein is cleared. The different types of classification is on the basis of accumulation of chylomicrons, elevated low density lipoprotein (LDL) concentration, abnormalities of Apo-E or increased very low density lipoprotein (VLDL) level due to obesity, overweight or diabetes (Havel et al., Hyperlipidemia therefore is a potent risk factor for atherosclerosis and coronary heart disease present in substantial proportion of young adults (Steinberg, 2005). According to data from National Health and Nutrition Examination Survey (NHANES), between 11.7% of adults aged 20-39 and 41.2% of adult aged 40-64 have elevated low density lipoprotein cholesterol (LDL-C) level (James et al., 2014). Studies on adults with familiar hypercholesterolemia have shown that, cardiovascular risk is increased early among those with high low density lipoprotein cholesterol (HLDL) level (Hopkins, 2003). Similarly, adults with extremely low LDL-C level conferred by genetic polymorphisms have significantly lower than average risk of cardiovascular disease (Sniderman et al., 2005). Populations consuming Ficus vogelii may likely have lower risk of cardiovascular disease as demonstrated in this study.

Hypercholesterolemia is a condition of excessively high plasma cholesterol level (American Heart Association, 2007). According to recent studies, hypercholesterolemia is considered to be a well established risk factor for coronary heart disease with elevated low density lipoprotein being the mechanism underlying it, with a high risk cholesterol serum level above 160mg/dl (The Expert Panel, 1988). In this study, the total plasma cholesterol concentration exceeded 140mg/dl in diabetic animals (DC), which was reversed to <120 mg/dl upon treatment with extract of *Ficus vogelii*.

Primary hypercholesterolemia is in general believed to be the result of reduced activity of LDL receptors (Brown & Goldstein 2006). Total cholesterol can be broken down into a diagnostic lipoprotein profile including high density lipoprotein (HDL), intermediate density lipoprotein (IDL), very low density lipoprotein

(VLDL), chylomicron remnants and triglycerides (American Heart Association, 2007). High density lipoprotein is considered to be beneficial as high levels of HDL-c have been correlated with reduced risk of negative cardiovascular event (Segrest et al., 1999, 2002). On the other hand, elevated level of low density lipoprotein cholesterol and triglycerides are considered detrimental to health as their elevated concentration in plasma has been correlated with poor cardiovascular outcomes (Segrest et al., 1999). Also, intermediate density lipoprotein, very low density lipoprotein and chylomicron remnants have been reported to potentially play an active role in peripheral vascular and coronary artery disease development (Segrest, 2002). The significant reduction of these types of lipoproteins caused by treatment of diabetic rats with extract of Ficus vogelii, strongly confirms the claims of populations using the plant in Nigeria for the treatment of diabetes (Kannel et al., 1979; Snidermann et al., 1991).

Cholesterol has been shown to interrupt and alter vascular structure and function as it builds within the lining of the vascular walls, thus interfering with endothelial function and leading to lesion and plaques (Kannel et al., 1979; Snidermann et al., 1991; Steinberg, 2005, 2006). Therefore elevation of hypercholesterolemia in diabetes may be associated with endothelial dysfunction and dislipidemia (Kannel et al., 1979; Snidermann et al., 1991).

Pharmacological treatment of hypercholesterolemia with simvastatin in a survival study compared with placebo, using 20mg to 40mg daily to simvastatin reduces serum total cholesterol by 25%, serum LDL-C by 35% and serum triglyceride by 10% and increases serum HDL-C (high density lipoprotein cholesterol) by 8% (Pedersen et al., 1998).

In this study, the effect of ethanolic extract of mature leaf of *Ficus vogelii* on dyslipidemia (hyperlipidemia and hypercholesterolemia), predisposed by artificially induced diabetes, using streptozotocin, was evaluated in laboratory animals, and the treatment was shown to be effective in reversing dyslipidemia. The results were consistent with earlier results using plant extracts as alternative to otherwise very expensive and unaffordable drugs (Ebong et al., 2008).

Plant extracts, including extracts from *Ficus vogelii* have been demonstrated to be effective in the treatment of dyslipidemia associated with diabetes mellitus. The

management of diabetes is a major worldwide problem because treatment with synthetic drugs results in adverse effects, and therefore, there have been concerted efforts worldwide to develop safer and more effective antidiabetic drugs from plant sources.

Studies have shown that treatment with plant extracts or drugs isolated from plants have beneficial effect in shielding β -cells from being damaged in non-insulin dependent type 1 diabetes, while plasma insulin concentration function to decrease serum glucose levels in insulin-dependent type 1 diabetes. Elevated serum lipids and lipoproteins concentration are some of the characteristics of uncontrolled diabetes. Type 2 diabetes is commonly associated with dyslipidemia which is a risk factor of cardiovascular disease.

Induction of diabetes in this present study resulted in a marked increase in the lipid content of diabetic rats. It was suggested that this may be due to increased mobilization of free fatty acids from peripheral muscles into the general circulation and plasma. Consequently, there was a significant decrease in HDL-C concentration with a significant rise in total cholesterol, triglycerides, LDL-C and VLDL-C concentrations. These results are consistent with observed concentrations of lipids and lipoproteins in an earlier study using animal models (Akpaso et al., 2013).

The treatment of animals in this condition with extract of Ficus vogelii reversed the disturbances in lipid concentrations and significantly (p<0.05) decreased lipid and cholesterol concentrations of VLDL, LDL and TC, while the concentration of HDL-c increased. This is an indication that the risk of cardiovascular disease in FV treatment in humans may be minimal. There were similarities between the activities of extract of Ficus vogelii and the standard drug (Metformin). The metformin treated group showed a significant change in the lipid profile of diabetic rats, showing a decrease in LDL, VLDL and total cholesterol, and an increase in serum high density lipoprotein. In a separate study, Egbuna et al. (2011), had demonstrated antihepatotoxic effectiveness of ethanolic extract of Ficus vogelii on liver function indices of CC14 induced hepatotoxicity.

Diabetes which is characterized by hyperglycemia has injurious effect both direct and indirect effects on the human vascular tree which are the major source of morbidity and motility in both type 1 and type 2

diabetes. These injurious effect are separated into macrovascular complications such as coronary artery disease, peripheral arterial disease and stroke, and secondly microvascular complications such as diabetic nephropathy, neuropathy and retinopathy (Micheal, 2008).

Insulin mobilization causes excessive mobilization of free fatty acid, under utilization of chylomicrons and very low density lipoproteins (VLDL) leading to hypertriacylcerolemia (Perdersen et al., 1998). Fatty acids undergo incomplete oxidation thus resulting in over production of ketone bodies. The formation of these ketone bodies produces carboxylic acid which ionizes, releasing protons and therefore, in uncontrolled diabetes the capacity of the bicarbonate buffering system of the blood is overwhelmed by these reactions, leading to acidosis and a consequent life threatening condition known as ketoacidosis (Nelson and Cox, 2000). Extracts of FV, containing phenolic and polyphenolic compounds and flavonoids, as well as saponins, act anti-oxidatively to neutralize excess carboxylic acid and acidosis condition in plasma, and sequested protons generated from the ionization reactions of the carboxylic acids.

Unlike synthetic drugs, plant extracts involved in ethnopharmacological management and treatment of hyperlipidemia and dyslipidemia do not lead to side effects such as myositis, gastric irritation, flushing dry skin and abnormal liver function. Thus plant extracts or herbal medicines, have advantages of being readily available, effective, safe, affordable and acceptable (Kan and Nylen, 1999). Synthetic drugs used for the treatment of anti-hyperlipidemic conditions have been implicated in the development of ischemic heart disease or the occurrence of further cardiovascular or cerebrovascular diseases (Davey and Pekkanen, 1992). Currently used hypolipidemic drugs are associated with so many adverse effects and withdrawal is associated with rebound phenomenon which is not observed with herbal medicinal preparations (Kan and Nylen, 1999).

Conclusion

It is noted in the present study that there is alteration in the triglyceride, very low density lipoprotein and high density lipoprotein serum concentration following induction of diabetes in the albino wistar rat. The serum TG, VLDL and VLD increased and HDL decreased in the diabetic control but on treatment with extract of *Ficus vogelii*, there was a decrease in triglyceride, Total

cholesterol, VLDL and LDL concentrations, and an increase in HDL-C. It was concluded that extract of *Ficus vogelii* suppressed hyperlipidemia and hypolipidemia and normalized dyslipidemia, confirming the ethno-medical claims that *Ficus vogelii* is effective in the treatment of cardiovascular diseases (CVDs).

Recommendation

Further research should be carried out on the plant to isolate, purify and characterize the active compounds, so as to understand which compound (s) that may be responsible for the biological activities observed in this study, and also to determine the effective therapeutic dose ED50 for further evaluation and toxicity studies in laboratory animals.

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