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Effects of *Uvaria chamae* Root Extracts on Blood Glucose, Inflammatory Markers, Lipid Profile, Liver and Renal Status in Streptozotocin–induced Diabetic Rats

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Summary: *Uvaria chamae* roots are traditionally used in the treatment of diabetes in many parts of the world, but the use of the extracts in the treatment of diabetes has not been scientifically validated. Thirty-six Sprague Dawley rats were assigned by weight into six groups [6 rats per group, average body weight 265.23 ± 7.20g]. Diabetes mellitus was induced by a single administration of streptozotocin (60 mg/kg) intraperitoneally. Normal and diabetic rats were treated with aqueous or ethanolic extract (300 mg/kg body weight/day/rat) of *Uvaria chamae* for 35 days. Rats were allowed free access to food, and extract added to the water bottle. Animals were euthanized on day 35 after an overnight fast and blood was collected for glucose, renal function, liver, serum lipid profile, and inflammatory markers assays. The blood glucose levels decreased by 38% and 53% in the diabetic rats administered aqueous or ethanolic extract respectively compared to an increase in the diabetic control (45%). The levels of TC, TG, LDL-C, VLDL-C, TG/HDL-C, and non-HDL-C were decreased in untreated rats, while the HDL-C was increased when the extracts were administered. There was a diminishing trend in IL-6, TNF-α and IL-1β levels in the treated diabetic groups. Serum creatinine level was slightly elevated in the diabetic group administered ethanolic extract. Overall, the consumption of *Uvaria chamae* extracts lowered blood glucose levels, lipid profile and increased HDL-C, while the IL-6 was decreased. The non-significant changes in renal function parameters indicated no adverse effects on the kidney in this short-term study.

Keywords*:* Blood glucose, Diabetes, Inflammation, *Uvaria chamae*

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INTRODUCTION

Diabetes mellitus is characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Sustained hyperglycemia is associated with the development of diabetic complications in patients with the disease (Makita *et al*., 1991). It is estimated that 552 million people will be diagnosed with the disease by 2030 (Whiting *et al*., 2011). Inflammatory cytokines are believed to exert central roles in the development of renal disease in diabetic patients (Navarro-Gon'zalez *et al*., 2011). Hyperglycemia can induce the expression of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), leading to the development of chronic subclinical inflammatory status in diabetes mellitus (Goldberg, 2009). Interestingly, IL-6 a crucial pro-inflammatory cytokine can promote insulin secretion at low concentration (Os'orio, 2015). A high level of IL-6 may damage β-cells and promote apoptosis (Oh *et al*., 2011). Interleukin-6 has also been reported to increase lipolysis in adipocytes as well as the release of free fatty acids that may affect mitochondria and glucose transporter 2 (GLUT-2) function and insulin sensitivity (Dessein *et al*., 2002). An increased IL-6 expression accompanies abnormal glucose metabolism (Huan *et al*., 2016). Hyperglycemia increases the generation of free radicals by auto-oxidation of glucose, and the increase in free radicals may lead to cell damage (Sharma *et al*., 2006). Alteration in serum lipid profile in people with diabetes has been reported to increase the risk of coronary heart disease (Massing *et al*., 2001). In the diabetic state, prolonged hyperglycemia may result in metabolic complications which will potentiate the release of reactive radical, that could interfere with the integrity of liver cells. For example, uncontrolled diabetes mellitus has been reported to be associated with elevated liver enzymes (Kim *et al*., 2006). There is currently no cure for diabetes mellitus, but there is an increasing demand for natural products with antidiabetic activities. Medicinal plants have been extensively used as an alternative medicine for the

management of diabetes mellitus (Mahalingam and Krishnan, 2008). *Uvaria chamae* is a medicinal plant found mostly in the tropical rain forest of West Africa. In Nigeria, it is used for the treatment of diabetes, diarrhea, hypertension, cough, hemorrhoids, kidney and bladder diseases (Hufford and Lasswell, 1976). It is commonly known as finger root or bush banana and belongs to the family *Annonaceae*. When ripe, the fruits are yellow and have a sweet pulp that is widely eaten. All parts of the plant are fragrant with widespread medicinal use in West Africa (Omajali *et al*., 2011). However, there is a shortage of scientific evidence to validate the beneficial role of the plant extract in the management of diabetes mellitus. In this study, the effects of the aqueous or ethanolic extract of the root on blood glucose, inflammatory cytokines, lipid profile, liver and renal functions in normal and diabetic rats were evaluated.

MATERIALS AND METHODS

Diabetes mellitus is characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Sustained hyperglycemia is associated with the development of diabetic complications in patients with the disease (Makita *et al*., 1991). It is estimated that 552 million people will be diagnosed with the disease by 2030 (Whiting *et al*., 2011). Inflammatory cytokines are believed to exert central roles in the development of renal disease in diabetic patients (Navarro-Gon'zalez *et al*., 2011). Hyperglycemia can induce the expression of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), leading to the development of chronic subclinical inflammatory status in diabetes mellitus (Goldberg, 2009). Interestingly, IL-6 a crucial pro-inflammatory cytokine can promote insulin secretion at low concentration (Os'orio, 2015). A high level of IL-6 may damage β-cells and promote apoptosis (Oh *et al*., 2011). Interleukin-6 has also been reported to increase lipolysis in adipocytes as well as the release of free fatty acids that may affect mitochondria and glucose transporter 2 (GLUT-2) function and insulin sensitivity (Dessein *et al*., 2002). An increased IL-6 expression accompanies abnormal glucose metabolism (Huan *et al*., 2016). Hyperglycemia increases the generation of free radicals by auto-oxidation of glucose, and the increase in free radicals may lead to cell damage (Sharma *et al*., 2006). Alteration in serum lipid profile in people with diabetes has been reported to increase the risk of coronary heart disease (Massing *et al*., 2001). In the diabetic state, prolonged hyperglycemia may result in metabolic complications which will potentiate the release of reactive radical, that could interfere with the integrity of liver cells. For example, uncontrolled diabetes mellitus has been reported to be associated with elevated liver enzymes (Kim *et al*., 2006). There is currently no cure for diabetes mellitus, but there is an increasing demand for natural products with antidiabetic activities. Medicinal plants have been extensively used as an alternative medicine for the management of diabetes mellitus (Mahalingam and Krishnan, 2008). *Uvaria chamae* is a medicinal plant found mostly in the tropical rain forest of West Africa. In Nigeria, it is used for the treatment of diabetes, diarrhea, hypertension, cough, hemorrhoids, kidney and bladder diseases (Hufford and Lasswell, 1976). It is commonly known as finger root or bush banana and belongs to the family *Annonaceae*. When ripe, the fruits are yellow and have a sweet pulp that is widely eaten. All parts of the plant are fragrant with widespread medicinal use in West Africa (Omajali *et al*., 2011). However, there is a shortage of scientific evidence to validate the beneficial role of the plant extract in the management of diabetes mellitus. In this study, the effects of the aqueous or ethanolic extract of the root on blood glucose, inflammatory cytokines, lipid profile, liver and renal functions in normal and diabetic rats were evaluated.

RESULTS

Biochemical Assessment

There were no significant changes ($p > 0.05$) in the food consumed (Table 1) and body weight of the rats in this study (Table 2). There were decreases of 38% and 53% in fasting blood glucose in the diabetic rats administered aqueous or ethanolic extract respectively compared to the increase in the diabetic control (45%) group. The administration of aqueous or ethanolic extract in normal rats resulted in slight decreases in fasting blood glucose of 0.2% and 4% respectively compared to the increase in normal control (11%) group. This study showed that BUN was significantly ($p<0.05$) increased in the diabetic control compared to normal control. In contrast, serum creatinine was non-significantly increased in the diabetic group administered ethanolic extract in comparison to normal control (Table 3).

The administration of aqueous or ethanolic extract to the normal and diabetic rats showed a decrease in total TC, TG, TG/HDL-C ratio, LDL-C, VLDL-C and non-HDL-C when compared to their respective controls

Table 1:
Food intake (g/week) by normal and diabetic rats administered aqueous or ethanlic extract of *Uvaria chamae*.

Group	Food Intake (g)
Normal Control	248.26 ± 44.22
Normal + Aq. Extract	249.27 ± 26.21
Normal + Eth. Extract	243.29 ± 43.13
Diabetic Control	405.55 ± 27.90
Diabetic + Aq. Extract	303.74 ± 74.31
Diabetic + Eth. Extract	381.29 ± 10.64

Values are means ± SEM of 4-6 determinations, and they were not significantly (p > 0.05) different among the groups. Eth= Ethanolic. Aq= Aqueous.

Table 2: Rats weight (g) for the duration (35 days) of study

Group	Initial Weight (g)	Final Weight (g)	Weight Change (%)
Normal Control	264.64 ± 24.01	314.12 ± 43.03	18.70
Normal + Aq. Extract	261.16 ± 16.90	306.33 ± 31.01	17.32
Normal + Eth. Extract	256.88 ± 18.70	287.48 ± 27.00	11.91
Diabetic Control	252.75 ± 25.11	235.07 ± 31.51	-6.90
Diabetic + Aq. Extract	274.58 ± 18.92	265.63 ± 31.30	-3.30
Diabetic + Eth. Extract	301.75 ± 3.41	247.00 ± 6.62	-18.11

Values are mean ± SEM of 4-6 determinations, and they were not significantly ($p > 0.05$) different among the groups. Eth= Ethanolic. Aq= Aqueous.

Table 3: Kidney function parameters (uric acid, BUN and creatinine) in the serum of normal and diabetic rats administered aqueous or ethanolic extract of *Uvaria chamae.*

Group	Uric Acid (mg/dL)	BUN (mg/dL)	Creatinine (mg/dL)
Normal Control	7.38 ± 1.01	28.66 ± 2.22	1.27 ± 0.02
Normal + Aq. Ext	12.41 ± 2.02	30.50 ± 5.40	1.25 ± 0.11
Normal + Eth. Ext	10.21 ± 2.50	32.00 ± 1.91	1.48 ± 0.10
Diabetic Control	7.05 ± 0.21	70.87 ± 6.62	1.82 ± 0.21
Diabetic + Aq. Ext	6.75 ± 0.71	70.75 ± 5.00*	1.68 ± 0.20
Diabetic + Eth. Ext	5.98 ± 0.20	77.87 ± 8.02*	1.92 ± 0.40

Values are some indices of renal function in mg/dl and are expressed as mean ± SEM.
*Vertical * denotes significant differences ($p < 0.05$) from normal control (Duncan Multiple Range Test). BUN = Blood Urea Nitrogen, Aq. Ext = Aqueous Extract, Eth. Ext = Ethanolic Extract*

Table 4: Blood lipid profile in Normal and Diabetic rats treated with *Uvaria chamae* extract.

Group	TC (mg/dL)	TG (mg/dL)	HDL-C(mg/dL)	TG/HDL-C	LDL-C (mg/dL)	VLDL-C (mg/dL)	Non-HDL-C (mg/dL)
Normal Control	117.26 ±1.70	80.39 ± 4.81	3.10 ± 0.31	38.81 ± 5.42	90.40±3.82	17.85±1.21	108.25±3.81
Normal + Aq. Ext	89.64 ± 2.31	48.23 ± 4.72	3.24 ± 0.32	22.07 ± 2.81	82.05±3.61	11.11±1.60	93.17±4.40
Normal + Eth. Ext	81.45 ± 6.52*****	36.94 ± 4.63	4.82 ± 0.31	72 ± 0.99*****	79.94±5.30	8.37±1.21	81.98 ± 6.11
Diabetic Control	133.16 ± 9.92	204.87±44.90	8.18 ± 0.60	26.70 ± 5.51	94.40±13.3	35.54±8.31	125.10±9.10
Diabetic + Aq. Ext	104.09 ±8.70	165.78 ±58.82	7.25 ± 0.41	14.83 ± 2.41	74.76±3.01	26.22±6.13	108.10±9.91
Diabetic + Eth. Ext	107.41±18.41	121.59 ± 27.90	11.28±0.40#	12.00 ± 0.30	70.61±7.40	20.86±4.70	98.57±15.50

*Values are serum concentrations of lipid profile (TC, TG, HDL-C, LDL-C, VLDL-C and non-HDL-C) in mg/dl and are expressed as mean ± SEM. Vertical * denotes significant differences ($p < 0.05$) from normal control, whereas # denotes significant differences ($p < 0.05$) in diabetic groups treated with Uvaria chamae extract when compared to diabetic control (Duncan Multiple Range Test). Aq. Ext= Aqueous Extract. Eth. Ext= Ethanolic Extract.*

(Table 4). The HDL-C was significantly ($p < 0.05$) increased in the diabetic group administered ethanolic extract when compared to diabetic control. There was a significant decrease in the concentration of ALT and ALP in the diabetic groups administered ethanolic and aqueous extracts when compared to their respective controls (Table 5). There was a significant ($p<0.05$) decrease in IL-6 and TNF-α in the Diabetic + Aq. Ext group compared to the Diabetic Control. While in the Diabetic + Eth. Ext, the IL-1β was significantly ($p<0.05$) reduced with a corresponding decrease in IL-6 and TNF-α when compared to the diabetic control (Table 6)

Histopathological findings in pancreas (figure 1) showed exuberant islet [A] and exocrine glands [B] in the pancreas of rats treated with aqueous or ethanolic extracts [plates 2 and 3] when compared to the normal control [plate1]. There was vascular congestion [A], vascular wall thickening and luminal narrowing [B] and mild infiltrates of chronic inflammatory cells in the pancreas of untreated diabetic rats [plate 4]. The pancreas of diabetic rats treated with aqueous or ethanolic root extract of *Uvaria chamae* showed resurgence of islet cells [A] and mild vascular congestion [B] [plates 5 and 6]. However, there was a mild ductal protein deposit [C] in plate 6. (H&E x 400).

The liver of rats treated with aqueous or ethanolic extract at 300 mg/kg body weight (figure 2) showed mild vascular congestion [A] plate 8, portal congestion [A] and moderate Kupffer cells [B] activation [plate 9] when compared to normal control [plate7]. . There were vascular congestion and dilatations [A] in the diabetic group treated with aqueous extract [plate 11], and vascular congestion [A] and moderate Kupffer cell activation [B] in the diabetic rats administered ethanolic extract [plate12] when compared to the diabetic control [plate 10]. (H&E x 400)

Table 5:
Liver function test (ALP, ALT, AST) in the serum of normal and streptozotocin- induced diabetic rats

Group	ALP(U/L)	ALT(U/L)	AST(U/L)
Normal Control	34.55 ± 7.06	43.94 ± 1.32	2.32 ± 0.52
Normal + Aq. Ext	28.79 ± 3.31	11.64 ± 1.31*	1.52 ± 0.21
Normal + Eth. Ext	34.20 ± 4.20	1.96 ± 0.21*	3.27 ± 0.80
Diabetic Control	188.87 ± 32.21	15.71 ± 8.70	3.49 ± 1.71
Diabetic + Aq. Ext	84.26 ± 23.01 #	17.46 ± 4.80	3.49 ± 1.02
Diabetic + Eth. Ext	96.74 ± 13.82 #	2.91 ± 0.21#	1.74 ± 0.01

*Values are means ± SEM of 4-6 determinations. Vertical * denotes significant difference ($p < 0.05$) from normal control, whereas # denotes significant difference ($p < 0.05$) in diabetic groups treated with Uvaria chamae extract when compared to diabetic control. Aq. Ext = Aqueous Extract, Eth. Ext = Ethanolic Extract.*

Table 6: Inflammatory markers (IL-6, IL-1β and TNF-α) in serum of normal and Streptozotocin- induced diabetic rats.

Group	IL-6 (pg/mL)	IL-1β (pg/mL)	TNF-α (pg/mL)
Normal Control	156.85 ± 11.01	113.75 ± 43.82	121.67 ± 19.50
Normal + Aq. Extract	152.17 ± 13.20	203.85 ± 14.81	360.03 ± 27.41
Normal + Eth. Extract	194.51± 38.61	183.15 ± 3.61	242.38 ± 10.42
Diabetic Control	316.99 ± 4.51	592.27 ± 25.50	725.09 ± 75.10
Diabetic + Aq. Extract	84.04 ± 16.50#	471.72 ± 76.20	149.01 ± 11.30 #
Diabetic + Eth. Extract	222.13 ± 33.10	201.42 ± 32.91#	503.66 ± 39.11

Values are means ± SEM of 4-6 determinations. Vertical #denotes significant differences ($p < 0.05$) in diabetic groups treated with Uvaria chamae extract when compared to diabetic control (Duncan Multiple Range Test). Eth= Ethanolic. Aq= Aqueous. IL = Interleukin, TNF-α = Tumor Necrosis Factor Alpha.

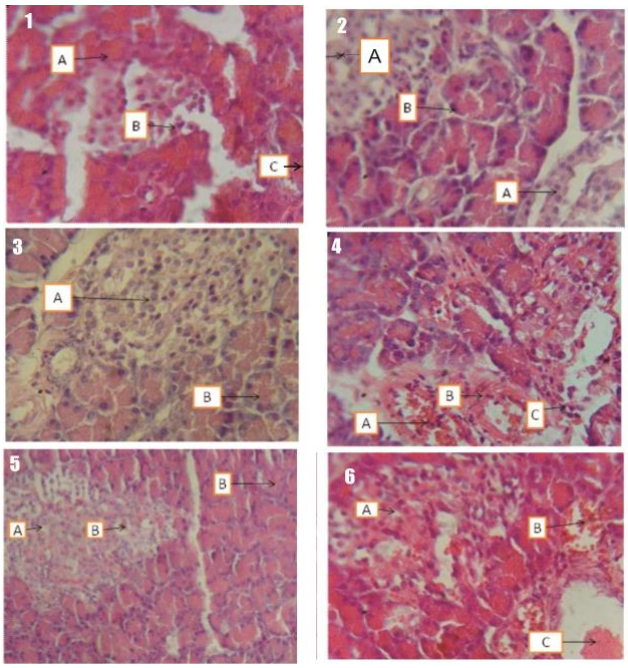

Figure 1.
Histopathologically findings in pancreas. Control pancreas [plate 1] showed exocrine glands [A], islets of Langerhans [B] and interlobular ducts. The pancreas of rats treated with 300 mg/kg aqueous extract [plate 2] showed exuberant islet [A] and exocrine glands [B]. Plate 3 is pancreas that was treated with 300 mg/kg of ethanolic extract showing exuberant islet [A] and exocrine glands [B]. The diabetic control pancreas [plate 4] showed severe vascular congestion [A], vascular wall thickening and luminal narrowing [B] and mild infiltrates of chronic inflammatory cells [C]. Plate 5 is the diabetic pancreas treated with 300 mg/kg aqueous extract showing resurgent islet [A] and mild vascular congestion [B]. While, plate 6 is the diabetic pancreas treated with 300 mg/kg ethanolic extract and showed resurgent islets [A], moderate vascular congestion [B] and mild ductal protein deposit [C]. (H&E x 400)

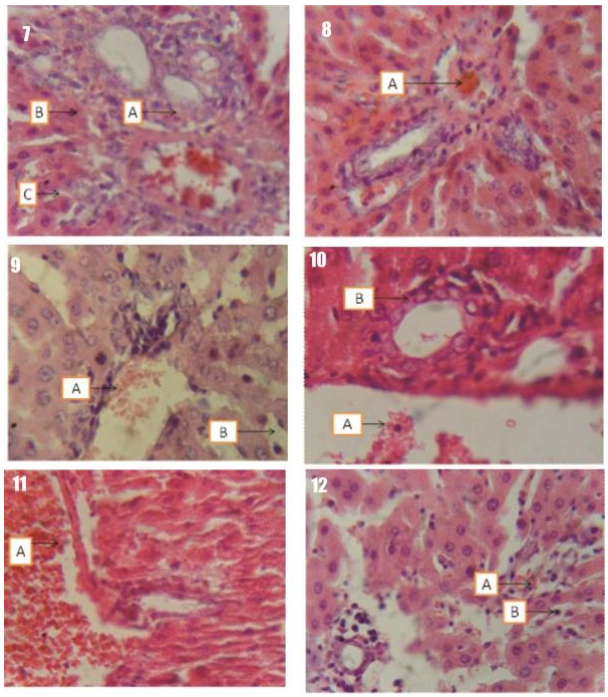

Figure 2.
Histopathological findings in liver. Control liver [plate 7] showed bile duct [A], hepatocyte [B] and sinusoids [C]. The liver of rats treated with 300 mg/kg aqueous extract [plate 8] showed mild vascular congestion [A]. The liver of rats treated with 300 mg/kg of ethanolic extract [plate 9] showed portal congestion [A] and moderate Kupffer cells activation [B]. Plate 10 is the liver of diabetic control rats which revealed portal congestion and dilation [A], and periportal infiltrates of chronic inflammatory cells [B]. In the diabetic liver treated with 300 mg/kg of aqueous extract [plate11] showed vascular congestion and dilation [A], while plate 12 is diabetic liver treated with 300 mg/kg of ethanolic extract showing vascular congestion [A] and moderate Kupffer cell activation [B]. (H&E x 400)

DISCUSSION

Streptozotocin has been an agent of choice to induce experimental diabetes mellitus due to its ability to cause specific necrosis of the pancreatic beta cells resulting in degranulation and loss of capacity to secrete insulin (Bastaki, 2005). In the present study, the intraperitoneal injection of streptozotocin resulted in the significant increase in the blood glucose levels. Andrade-Cetto *et al*., 2019 reported the hypoglycemic effects of *Croton guatemalensis, Solanum americanum Mill and Neurolaena lobate*. While, Karunanayake *et al*., 1984 also reported the hypoglycemic effect of aqueous decoction of *Aegle marmelos* root bark in normal fasted rats. In this study, the administration of the aqueous or ethanolic extract of *Uvaria chamae* to the diabetic animals significantly decreased blood glucose which supports the traditional use of the extracts in the management of the disease. Diabetic control rats lost body weight when compared to the diabetic groups treated with the aqueous or ethanolic extract of *Uvaria chamae*. The decrease in body weight in the untreated diabetic rats may be attributable to gluconeogenesis with the associated increase in muscle wasting and loss of proteins in tissues (Shirwaikar *et al*., 2006). The observed increase in body weight of the treated diabetic rats may be a reflection of the ability of *Uvaria chamae* to promote cellular utilization of glucose with a subsequent decrease in blood glucose levels. The observed increasing trend in food intake in the diabetic control rats may be due to their inability to metabolize glucose for energy generation.

Abnormalities in kidney function progress by an alteration in hemodynamics that may lead to proteinuria, glomerulosclerosis and renal dysfunction (Zafar and Naqvi, 2010). The ability to overcome renal haemodynamic abnormality and the reduction of proteinuria is essential in preventing the decline of kidney function. Protein and nucleic acid metabolism result in the formation of non-protein nitrogenous compounds (Firdous *et al*., 2013). A significant elevation in serum creatinine, uric acid, and BUN levels is indicative of impaired renal function in people with diabetes (Mustafa *et al*., 2012). In oxidative stress, uric acid preserves the ability of vascular dilatation of the endothelium and prevents alteration of endothelial enzyme levels (Palsamy and Subramanian, 2008). The observed non-significant increase in BUN and creatinine, and lowered serum uric acid levels in diabetic rats administered aqueous or ethanolic extract of *Uvaria chamae* is an indication that the kidney function parameters may not be adversely affected in short-term use. However, long-term usage of the extracts should be done with caution as the extracts may adversely renal function. It has been reported that the conversion of streptozotocin to metabolites in the liver can result in catalytic membrane phospholipid peroxidation which ultimately reduces lipid export from the liver cells (Kumar *et al.*, 2007). The observed increase in TC, TG, LDL-C, and VLDL-C in the diabetic control rats may be associated with streptozotocin administration, which could be due to portal congestion, dilatation and periportal infiltrates of chronic inflammatory cells as observed histopathologically. Sphepherd (2005), reported that reduced HDL-C level in diabetic control rats is associated with insufficiency in fatty acid metabolism, and consequently result in hypercholesterolemia and hypertriglyceridemia which are standard features of lipid abnormalities in diabetes. Non- HDL cholesterol has been shown to be a predictor of cardiovascular risk (Virani, 2011), and contains cholesterol of all atherogenic particles (Grundy, 2002). A high TG/HDL-C ratio has been reported to be associated with several metabolic derangements like insulin resistance (Gonzalez-Gonzales-Chavez *et al*., 2011), beta cell dysfunction (Maturu *et al*., 2015) and diabetes incidence (Vega *et al*., 2014). In this study, we noted the enhancement of lipid profile constituents in the diabetic rats treated with aqueous or ethanolic extract of *Uvaria chamae*. Elevated liver enzymes are associated with diabetes mellitus (Kim *et al*., 2006), and prolonged hyperglycemia may result in metabolic complications through the release of reactive radicals that adversely alter the integrity of liver cells. The observed increase in ALP in the diabetic control may be associated with the cellular interaction of streptozotocin in the hepatocytes. Other workers have reported some liver pathology such as infiltration of nonspecific inflammatory cells which supports liver tissue damage in diabetic control seen in this study (Kumar *et al*., 2013; Khattab *et al*., 2013). However, the levels of ALP were significantly reduced by the extracts. We also noted a significant decrease in ALT activity in the diabetic rats treated with the ethanolic extract. However, the ethanolic extract was more effective in ameliorating the adverse effects of streptozotocin metabolites in the liver.

The observed elevated IL-6 expression positively correlated with glucose toxicity in the diabetic control group. However, there was a significant ($p<0.05$) reduction in IL-6 in the diabetic group administered aqueous, and a non-significant decrease in the diabetic group administered the ethanolic extract of *Uvaria chamae* when compared to the diabetic control. Similarly, the level of IL-1β in the diabetic group treated with ethanolic extract was significantly ($p<0.05$) reduced when compared to the diabetic control. Recently, attention has been focused on IL-1β, which is one of the primary pro-inflammatory cytokines that has been shown to cause tissue damage and organ failure. Thus, it is a crucial mediator in auto-inflammatory conditions (Dinarello, 2009; Dinarello *et al*., 2012). However, IL-1β is a vital role in Type 1 diabetes mellitus and has long been known to cause

pancreatic β-cell dysfunction and death (Mandrup-Poulsen *et al*., 2010). Interleukin-1β is produced and released by several cell types in response to tissue insult, or the case of diabetes mellitus, by pancreatic β-cells under hyperglycemic conditions (Maedler *et al*., 2002). Once present in the pancreatic environment it can act locally to inhibit insulin synthesis and secretion and induce pancreatic β-cell apoptosis. Hence, it is a promising target for diabetes therapeutic intervention (Mandrup-Poulsen *et al*., 2010). The administration of the aqueous or ethanolic extract of *Uvaria chamae* stimulates insulin release from the pancreas and prevent glucotoxicity in the microenvironment of β-cells of pancreas, thereby preventing its death as seen in the resurgence of islet cells. It has been reported that TNF-α is a possible mediator of insulin resistance and diabetes mellitus since it inhibits insulin signaling and impairs its secretion (Brunetti *et al*., 2014). Increased plasma level of pro-inflammatory cytokine, TNF-α is associated with chronic disease in Type I diabetes (Domingueti *et al*., 2016). Tumor necrosis factor stimulates hepatic lipogenesis, increases VLDL production, and raises serum lipid levels in diabetics (Feingold *et al*., 1990). Advanced glycosylation products have been shown to stimulate the production of TNF-α by macrophages (Vlassara *et al*., 1988). The data from this study showed a significant ($p<0.05$) reduction in the level of TNF-α in the diabetic group administered aqueous extract of *Uvaria chamae* in comparison to the untreated diabetic animals. Hence, the extract may have the ability to enhance insulin signaling and secretion from the β-cells of the pancreas, thereby preventing the complications associated with inflammatory conditions in diabetes mellitus. Histologically, the resurgence of islets of Langerhans in the diabetic rats administered aqueous or ethanolic extract when compared to diabetic control is supported by the significant ($p<0.05$) decrease in blood glucose observed in this study.

Overall, the consumption of aqueous or ethanolic extract of *Uvaria chamae* lowered blood glucose levels, lipid profile, and upregulation of the HDL-C which may be beneficial in the management of diabetes mellitus. The extracts administration especially the aqueous extract reduced the inflammatory cytokine (IL-6) that is commonly up-regulated in diabetes. Although the treatments in this short-term study did not significantly alter renal function, but the long-term use of the extracts should be done with caution.

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