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Studies on the Antidyslipidemic and Anti-Inflammatory Properties of Swertiamarin, a Major Secoiridoid Glycoside of *E. Littorale* Leaves Studied in High Fat Diet Fed-Low Dose Streptozotocin Induced Experimental Diabetes in Rats

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ABSTRACT: Insulin resistance precedes and predicts the onset of T2DM which is characterized by reduced insulin-stimulated glucose uptake, increased hepatic glucose production, enhanced lipolysis and altered insulin secretion. Chronic hyperglycemia associated with insulin resistance in type 2 diabetes is characterized by abnormalities in lipid and lipoprotein metabolism. In the present study, an attempt has been made to investigate the antidyslipidemic and anti-inflammatory properties of Swertiamarin, a major secoiridoid glycoside of *E. littorale* leaves in high fat diet fed-low dose streptozotocin induced experimental diabetes in rats. Oral administration of Swertiamarin to diabetic group of rats resulted in significant decrease in the levels of lipid contents in serum, hepatic and renal tissues. Likewise, the decreased levels of high-density lipoprotein cholesterol and increased levels of low density lipoprotein and very low density lipoprotein cholesterol in serum of diabetic rats were normalized. The increased levels of proinflammatory cytokines such as TNF α , IL β and IL-6 were significantly decreased. The altered levels of adiponectin and leptin were normalized. The nuclear levels of NF- κ B p65 unit, nitric oxide in diabetic group of rats was significantly decreased upon treatment with Swertiamarin. The data obtained evidenced the antidyslipidemic and antiinflammatory properties of Swertiamarin.

KEYWORDS: Swertiamarin; T2DM; Hypolipidemic; Antiinflammatory properties

I. INTRODUCTION

T2DM is a chronic, multisystemic metabolic disorder that is linked to a variety of genetic and environmental factors, often characterized by elevations in fasting blood glucose levels [1]. Insulin resistance precedes and predicts the onset of T2DM in susceptible humans and contributes to multiple metabolic derangements including reduced insulin-stimulated glucose uptake in insulin-sensitive tissues, increased hepatic glucose production, increased lipolysis in adipose tissue and altered insulin secretion [2]. Insulin resistance is known to increase the risk of developing cardiovascular complications in diabetes mellitus [3]. Diabetic dyslipidemia is characterized by increased triglycerides, low HDL-cholesterol, elevated LDL-cholesterol levels and the predominance of small dense LDL particles. The abnormalities in lipid and lipoprotein metabolism represent the major link between diabetes and the increased cardiovascular risk of diabetic patients. However, alterations of insulin sensitive pathways, elevated free fatty acids levels and low grade inflammation result in an overproduction and decreased catabolism of triglyceride rich

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lipoproteins of intestinal and hepatic origin [4]. The composition of lipoprotein particles in diabetic dyslipidemia is more atherogenic than in dyslipidemia in general. The factors such as effect of insulin in liver apoprotein synthesis, abnormal regulation of lipoprotein lipase (LPL), actions of cholesteryl ester transfer protein (CETP) and peripheral actions of insulin on adipocytes and muscle chiefly contribute to the development of diabetic dyslipidemia [5].

Type 2 diabetic individuals are often obese with central visceral adiposity. Hence, adipose tissue plays a chief role in the pathogenesis of type 2 diabetes. The global burden of T2DM continues to rise as the worldwide prevalence of adult diabetes is projected to increase to 380 million people by 2025. Reducing the incidence of obesity by lifestyle changes is considered as a primary objective of healthcare in diabetic individuals [6]. The cholesterol lowering role of statins and other compounds such as ezetimibe, fibrates, omega-3 fatty acids, bile acid sequestrants are often elicit undesirable side effects after prolonged use. Hence, search for medicinal plants or their bioactive components for the treatment of diabetic dyslipidemia continues.

Enicostemma littorale Blume (*E. littorale*) is a traditionally important medicinal plant widely used for the treatment of diabetes and its secondary complications. It belongs to the family *Gentianaceae*. Swertiamarin, a major secoiridoid glycoside, originally isolated from the leaves of *E. littorale* and was reported to be responsible for most of its medicinal properties. Most of the reports available in the literature pertaining to the pharmacological properties of Swertiamarin are based on *in vitro* studies. Recently, we have reported the antidiabetic properties of Swertiamarin in experimental type 2 diabetes [7]. In the present study, the antidyslipidemic potential of Swertiamarin was evaluated in HFD fed-low dose STZ induced type 2 diabetes in rats.

II. MATERIALS AND METHODS

Experimental Animals

Male, Wistar rats weighing about 160-180 g, procured from Tamilnadu Veterinary and Animal Sciences University, Chennai, India, were housed in polypropylene cages under standard vivarium conditions (12 h light/dark cycle) and temperature ($25 \pm 2^\circ\text{C}$) with *ad libitum* access to water and standard rat chow (Hindustan Lever Ltd., Bangalore, India) with a composition of 5% fat, 21% protein, 55% nitrogen-free extract and 4% fiber (w/w) with adequate minerals and vitamins for the animals. The animals were acclimatized to the laboratory conditions for 2 weeks prior to the inception of experiments. All animal experimentations were premeditated and executed in accordance with the ethical norms approval by Ministry of Social Justices and Empowerment, Government of India and Institutional Animal Ethics Committee Guidelines.

High Fat Diet fed – Low Dose Streptozotocin Induced Diabetes

The rats were divided into two dietary regimens by feeding either normal or high fat diet (HFD) for the initial period of two weeks. The ingredients and chemical composition of the HFD was followed as before reported [8]. After two weeks of dietary manipulation, the groups of rats fed with HFD were intraperitoneally injected with freshly prepared low dose of streptozotocin (35 mg/kg b.w.) dissolved in 0.1M ice cold citrate buffer, pH 4.5. One week after STZ administration, the experimental rats were screened for fasting blood glucose levels. Rats having fasting blood glucose (FBG) $>250\text{mg/dl}$ that exhibited random hyperglycemia and glycosuria were selected for the experiment. The rats were allowed to continue to feed on the respective diets until the end of the experiments.

Experimental Protocol

The rats were divided into four groups each group comprising six rats.

Group 1: Control rats

Group 2: Diabetic rats

Group 3: Diabetic rats treated with Swertiamarin (50 mg/kg b.w.)

Group 4: Diabetic rats treated with metformin (50 mg/kg b.w.)

At the end of the treatment period, the rats were fasted overnight, anaesthetized (ketamine, 80 mg/kg b.w. i.p.) and sacrificed by cervical decapitation. The blood was collected with or without anticoagulants for plasma or

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serum separation, respectively. The liver, kidney and pancreatic tissues were dissected out and washed in ice-cold saline and used for further experimental studies.

Analysis on Lipid Profile

The total lipids were extracted from the liver and kidney tissues [9]. The levels of cholesterol, triglycerides and free fatty acid levels in serum, liver and kidney tissues were estimated [10, 11 &12]. The levels of phospholipids were estimated by digestion with perchloric acid [13] and the phosphate liberated was estimated [14]. The levels of High-density lipoproteins (HDL), very low density lipoprotein (VLDL) and low-density lipoproteins (LDL) were separated from the serum according to dual precipitation technique [15,16] and the cholesterol content of the lipoproteins was estimated.

Assay of inflammatory markers

The NF- κ B/p65 Active ELISA kit (Imgenex, San Diego) was used to quantify NF- κ B free p65 in the nuclear fraction of pancreatic, liver and kidney tissues. The analysis was performed according to the manufacturer's instructions. Additionally, the levels of pro-inflammatory cytokines such as TNF- α , IL-1 β and IL 6 in plasma and tissues of control and experimental groups of rats were determined by specific ELISA kits according to the manufacturer's instructions (Biosource, Camarillo, CA, USA).

Determination of nitric oxide content

Nitric oxide (NO) level in serum was assayed indirectly by measuring the nitrite concentration by colorimetric method based on the Griess reaction [17].

III. RESULTS

Table 1 represents the effect of oral administration of Swertiamarin on the levels of cholesterol, triglycerides, phospholipids and free fatty acids in the serum of experimental groups of rats. The levels were significantly elevated in the HFD-STZ diabetic group of rats. Oral treatment of Swertiamarin restored the altered levels to physiological range in the diabetic group of rats.

Table 1: The levels of lipid profile of control and experimental rats after 30 days of experimental period

Groups	Cholesterol	Triglycerides	Phospholipids	Free fatty acids
Control	113.30 \pm 1.55	78.45 \pm 3.12	80.00 \pm 3.40	63.84 \pm 3.43
Diabetic	243.00 \pm 11.21 ^{a*}	173.00 \pm 13.00 ^{a*}	154.50 \pm 5.10 ^{a*}	145.40 \pm 4.53 ^{a*}
Diabetic + Swertiamarin	150.40 \pm 3.70 ^{b*}	120.12 \pm 5.33 ^{b*}	110.55 \pm 3.00 ^{b*}	96.58 \pm 4.20 ^{b*}
Diabetic + Metformin	134.00 \pm 3.32 ^{b*}	108.43 \pm 4.20 ^{b*}	108.13 \pm 3.39 ^{b*}	93.70 \pm 2.33 ^{b*}

Units: mg/dl. Values are given as mean \pm S.E.M for groups of six rats in each. One-way ANOVA followed by post hoc test LSD. The results were compared with ^aControl rats, ^bDiabetic rats. Values are statistically significant at *P<0.05

Tables 2 and 3 depict the effects of Swertiamarin on the levels of total cholesterol, triglycerides, phospholipids and free fatty acids in the liver and kidney tissues of experimental groups of rats. The levels of lipid profile were significantly elevated in the HFD-STZ diabetic group of rats when compared with control group of rats. However, oral administration of Swertiamarin as well as metformin to diabetic groups of rats lowered the levels to near normalcy.

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Table 2: Effect of Swertiamarin on the levels of total cholesterol (TC), triglycerides (TG), free fatty acids (FFA) and phospholipids (PL) in the hepatic tissues of experimental group of rats

Groups	TC	TG	FFA	PL
Control	8.25 ± 0.42	4.5 ± 0.24	7.08 ± 0.23	24.40 ± 1.81
Diabetic control	18.20 ± 0.74 ^{a*}	8.04 ± 0.42 ^{a*}	14.40 ± 0.63 ^{a*}	49.50 ± 2.32 ^{a*}
Diabetic + Swertiamarin	13.40 ± 0.56 ^{b*}	5.40 ± 0.25 ^{b*}	9.50 ± 0.42 ^{b*}	26.20 ± 1.24 ^{b*}
Diabetic + Metformin	10.50 ± 0.83 ^{b*}	4.70 ± 0.33 ^{b*}	8.54 ± 0.36 ^{b*}	24.10 ± 1.30 ^{b*}

Units are expressed as mg/g wet tissue. Values are expressed as mean ± SD (n = 6).

Statistical significance was compared within the groups as follows: ^acompared with control rats, ^bcompared with diabetic control. Values are statistically significant at *p<0.05.

Table 3: The levels of total cholesterol (TC), triglycerides (TG), free fatty acids (FFA) and phospholipids (PL) in the renal tissues of control and experimental group of rats

Groups	TC	TG	FFA	PL
Control	6.80 ± 0.43	6.80 ± 0.50	4.80 ± 0.35	20.39 ± 0.85
Diabetic control	16.60 ± 0.63 ^{a*}	8.20 ± 0.58 ^{a*}	16.41 ± 0.73 ^{a*}	32.41 ± 1.92 ^{a*}
Diabetic + Swertiamarin	10.45 ± 0.40 ^{b*}	7.75 ± 0.43 ^{b*}	7.58 ± 0.33 ^{b*}	22.10 ± 0.91 ^{b*}
Diabetic + Metformin	7.40 ± 0.34 ^{b*}	6.63 ± 0.31 ^{b*}	9.80 ± 0.42 ^{b*}	20.13 ± 1.32 ^{b*}

Units are expressed as mg/g wet tissue.

Values are expressed as mean ± SD (n = 6).

Statistical significance was compared within the groups as follows: ^acompared with control rats, ^bcompared with diabetic control.

Values are statistically significant at *p<0.05

The effect of oral administration of Swertiamarin on the levels of plasma lipoproteins such as HDL, LDL and VLDL cholesterol in experimental groups of rats were illustrated in Table 4. The levels of LDL and VLDL were elevated significantly with a reduction in the levels of HDL cholesterol in the HFD-STZ diabetic group of rats when compared to control rats. However, the altered levels of plasma lipoproteins in the HFD-STZ diabetic group of rats were normalized by the oral administration of Swertiamarin and the efficacy was comparable with metformin.

Table 4: The levels of HDL-Cholesterol, LDL-Cholesterol and VLDL-Cholesterol in serum of control and experimental groups of rats

Groups	HDL-C	LDL-C	VLDL-C
Control	37.50 ± 1.70	69.50 ± 4.60	18.45 ± 1.40
Diabetic control	13.42 ± 0.67 ^{a*}	210.00 ± 13.50 ^{a*}	36.20 ± 1.55 ^{a*}
Diabetic + Swertiamarin	27.05 ± 1.38 ^{b*}	120.10 ± 7.31 ^{b*}	24.70 ± 1.30 ^{b*}
Diabetic + Metformin	24.00 ± 1.50 ^{b*}	111.40 ± 6.80 ^{b*}	20.30 ± 1.11 ^{b*}

Units are expressed as mg/dL. Values are expressed as mean ± SEM [n = 6].

^aStatistical significance were compared with normal control rats.

^bStatistical significance were compared with diabetic group of rats.

Values are statistically significant at *p<0.05.

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Table 5: The levels of Adiponectin and Leptin in plasma of control and experimental groups of rats.

Groups	Adiponectin	Leptin
Control	7.00 ± 0.38	0.93 ± 0.05
Diabetic control	3.52 ± 0.30 ^{a*}	1.18 ± 0.07 ^{a*}
Diabetic + Swertiamarin	5.40 ± 0.21 ^{b*}	0.95 ± 0.06 ^{b*}
Diabetic + Metformin	4.9 ± 0.28 ^{b*}	0.83 ± 0.04 ^{b*}

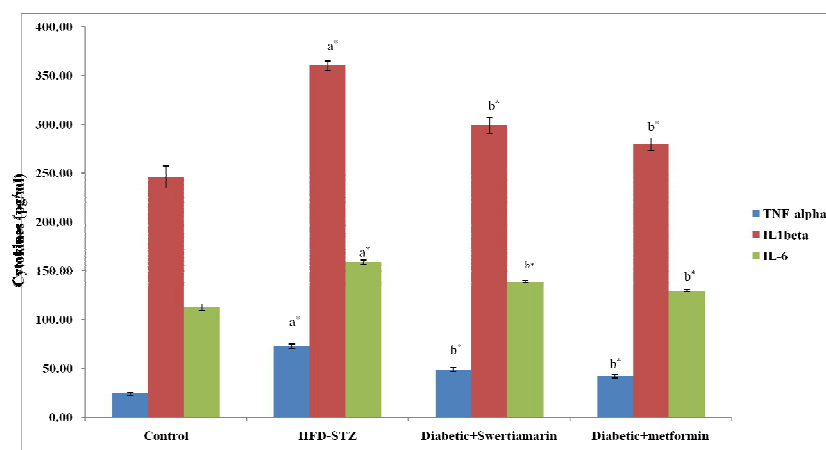
Unit as expressed as µg/ml for Adiponectin and ng/l for leptin.

Values are given as mean ± S.E.M for groups of six rats in each. One-way ANOVA followed by post hoc test LSD. Values are statistically significant at * $p < 0.05$. Statistical significance was compared within the groups as follows ^acompared to Control rats; ^bcompared to Diabetic rats.

The levels of adipokines such as adiponectin and leptin in the plasma are depicted in table 5. The level of plasma adiponectin is reduced, whereas the concentration of leptin is significantly increased in diabetic rats when compared to control group of rats. Upon treatment with Swertiamarin the altered levels were brought back to near normal level in diabetic rats.

The levels of TNF- α , IL-6 and IL-1 β in the plasma, hepatic and renal tissues of control and experimental groups of rats are presented as figure 1, 2 and 3 respectively. The levels of proinflammatory cytokines were significantly increased in the diabetic group of rats when compared with control rats. However, oral treatment with Swertiamarin as well as metformin for 30 days to HFD-STZ induced diabetic rats significantly decreased the levels of these proinflammatory cytokines to near physiological levels.

Figure 1: Effect of Swertiamarin on the plasma levels of TNF- α , IL-1 β and IL-6 in experimental groups of rats



Values are given as mean ± S.E.M [n=6] for groups of six rats in each. One-way ANOVA followed by post hoc test LSD. Statistical significance was compared within the groups as follows: ^acontrol rats; ^bdiabetic control rats; Values are statistically significant at * $p < 0.05$

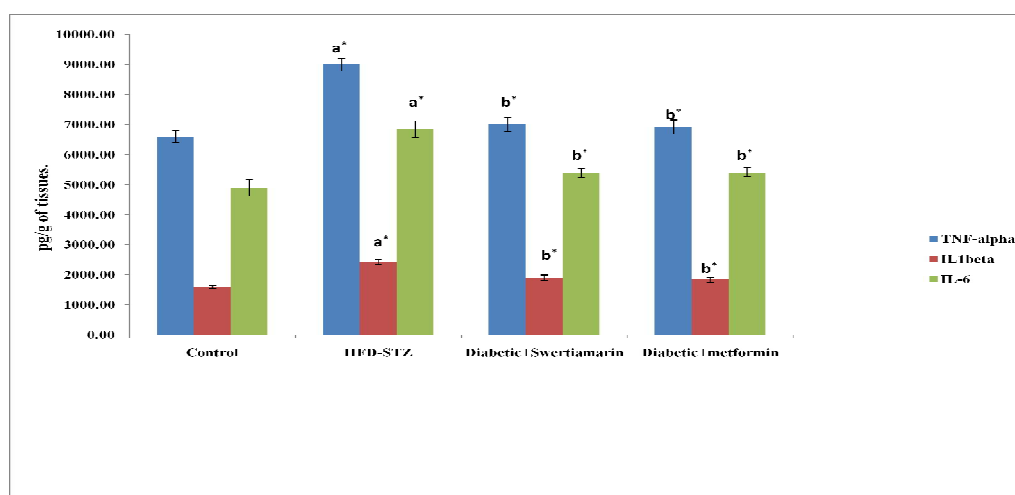
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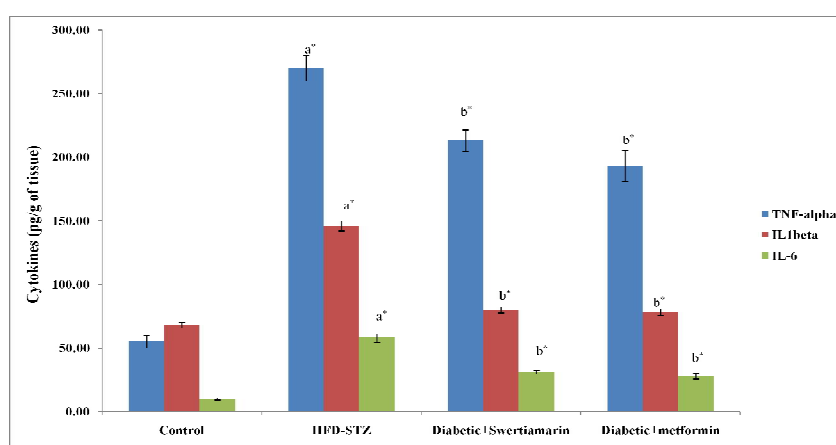
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Figure 2: Effect of Swertiamarin on the levels of TNF- α , IL β and IL-6 in hepatic tissues of experimental groups of rats



Units: pg/g of tissues. Values are given as mean \pm S.E.M [n=6] for groups of six rats in each. One-way ANOVA followed by post hoc test LSD. Statistical significance was compared within the groups as follows: ^acontrol rats; ^bdiabetic control rats; Values are statistically significant at ^{*} $p < 0.05$.

Figure 3: Effect of Swertiamarin on the levels of TNF- α , IL β and IL-6 in renal tissues of experimental groups of rats



Values are given as mean \pm S.E.M [n=6] for groups of six rats in each. One-way ANOVA followed by post hoc test LSD. Statistical significance was compared within the groups as follows: ^acontrol rats; ^bdiabetic control rats; Values are statistically significant at ^{*} $p < 0.05$.

The levels of NF- κ B free p65 unit in the nuclear fraction of pancreatic, hepatic and renal tissues of control and experimental groups of rats (Figure 4) and the levels of total nitric oxide in serum (Figure 5), hepatic and renal tissues (Figure 6) were depicted. The nuclear levels of NF- κ B p65 unit and Nitric oxide in diabetic group of rats were significantly escalated when compared to control group of rats. Oral administration of Swertiamarin as well as metformin to diabetic group of rats showed a marked decline in the level of NF- κ B p65 and Nitric oxide to near normal levels.

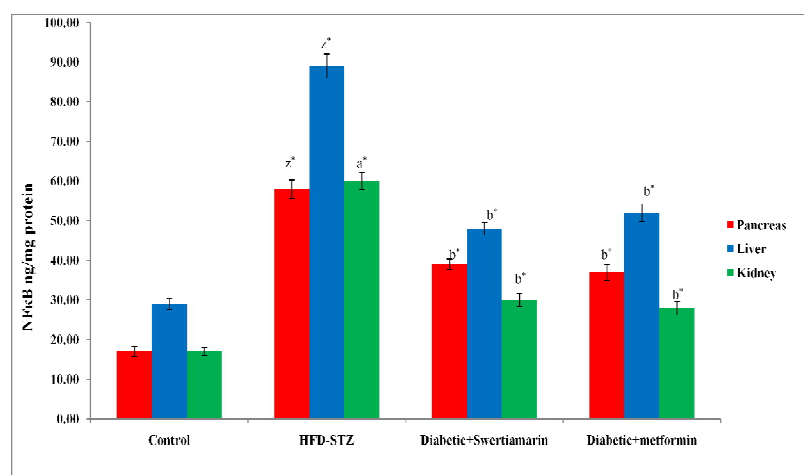
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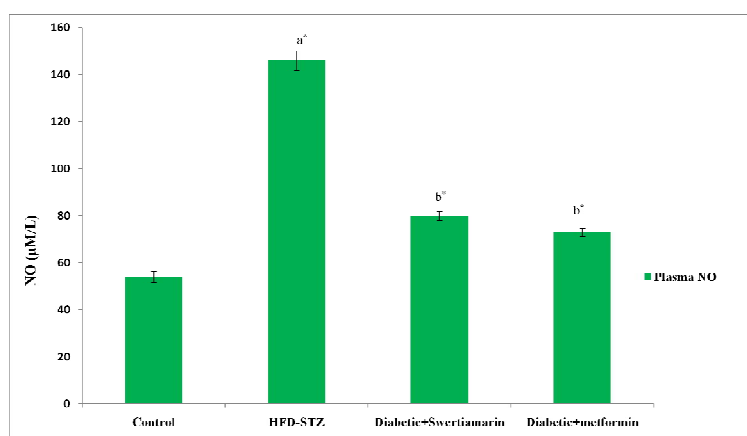
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Figure 4: Effect of Swertiamarin on the nuclear levels of NF- κ B p65 in Pancreas, Liver and kidney tissues of experimental groups of rats.



Values are given as mean \pm S.E.M [n=6] for groups of six rats in each. One-way ANOVA followed by post hoc test LSD. Statistical significance was compared within the groups as follows: ^acontrol rats; ^bdiabetic control rats; Values are statistically significant at * $p < 0.05$.

Figure 5: Effect of Swertiamarin on the levels of NO in plasma of experimental groups of rats



Values are given as mean \pm S.E.M [n=6] for groups of six rats in each. One-way ANOVA followed by post hoc test LSD. Statistical significance was compared within the groups as follows: ^acontrol rats; ^bdiabetic control rats. Values are statistically significant at * $p < 0.05$.

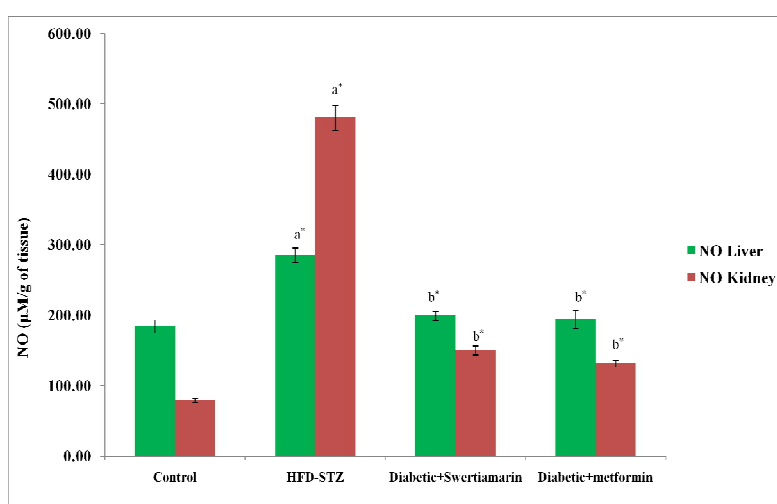
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Figure 6: Effect of Swertiamarin on the levels of NO in liver and kidney tissues of experimental groups of rats



Values are given as mean \pm S.E.M [n=6] for groups of six rats in each. One-way ANOVA followed by post hoc test LSD. Statistical significance was compared within the groups as follows: ^acontrol rats; ^bdiabetic control rats. Values are statistically significant at * $p < 0.05$.

IV. DISCUSSION

Diabetes mellitus is characterized by chronic hyperglycemia which arises due to insufficient insulin secretion coupled with insulin resistance resulting in disturbances in the metabolism of lipids, carbohydrates and proteins, in addition to extensive damage to insulin producing β -cells of the pancreas [8]. The major source of fuel for oxidative muscles such as heart and skeletal muscles are fatty acids. Recently, we have reported that oral administration of Swertiamarin at a concentration of 50mg/kg b.w./rat/day for 30 days to HFD fed – low dose STZ induced experimental type 2 diabetes significantly decreased the levels of fasting blood glucose and HOMA-IR indicating the antidiabetic effect of Swertiamarin. In continuation of our earlier findings, in the present study an attempt has been made to evaluate the effect of Swertiamarin on the levels of lipid profile and proinflammatory cytokines in HFD fed-low dose STZ induced diabetic rats [7].

Hypercholesterolemia and hypertriglyceridemia are the major risk factors arises due to chronic hyperglycemia in diabetes which often results in the initiation, progression and development of coronary heart disease, a major secondary complication of diabetes mellitus. Adipose tissue performs a wide range of metabolic as well as endocrine functions. Free fatty acids (FFAs) released from the adipocytes serve as the prime source of fuel in the post-absorptive state. Plasma FFA levels reflect a balance between release from the intravascular lipolysis of triglyceride-rich lipoproteins and the uptake of FFA predominantly re-esterified in adipose tissue as well as in liver and oxidized in muscle, heart, liver and other tissues. Thus, the levels of FFAs released from the adipose tissues can be considered as a marker for insulin resistance [18]. Increased free fatty acid flux from adipose tissue to non-adipose tissues especially liver resulting from abnormalities of fat metabolism, participates in increased synthesis and secretion of VLDL.

High plasma concentrations of triglyceride-rich lipoprotein and VLDL lead to an increase in the release of FFAs and generation of remnants as a result of lipolysis by the enzyme lipoprotein lipase. The increased VLDL level down regulates LDL receptor [19] resulting in increased proportion of LDL cholesterol particles [20], decreased HDL cholesterol level and elevated peripheral TG concentrations [21]. In the present study, the increased levels of circulatory FFAs and triglycerides in diabetic rats were significantly reduced upon oral treatment with Swertiamarin indicating its hypolipidemic properties.

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Cholesterol (both free and esterified forms) and triglycerides are the two main lipids in plasma. They are transported in lipoproteins, pseudomicellar lipid-protein complexes, in which the main apolipoproteins such as apo B-100/48, apo A-I, apo A-II, apo E, and the apo Cs are the integral components [22]. Apo B is a component of all atherogenic lipoproteins such as chylomicron remnants, VLDL and their remnants, IDL, lipoprotein (a) and LDL, whereas apo A-I and apo A-II are the components of HDL. In dyslipidemic individuals with cardiometabolic risk, the increased free fatty acid flux may represent a significant abnormality driving increased hepatic assembly and secretion of VLDL, IDL, and/or LDL particles [23]. In the present study, HFD-STZ induced diabetic rats showed significantly elevated levels of FFA, cholesterol and triglycerides in plasma, liver and kidney as well as increased levels of plasma LDL-cholesterol, VLDL-cholesterol and decreased HDL-cholesterol. Oral administration of Swertiamarin to diabetic rats significantly reversed the altered levels of lipid profile in plasma as well as in vital tissues when compared to diabetic rats. The anti-dyslipidemic property of Swertiamarin might be due to the increased uptake and oxidation of fatty acids as a result of enhanced activation of AMPK in peripheral tissues especially in skeletal muscles.

Adipose tissue despite being a lipid storage site, it also functions as a paracrine and endocrine organ which secretes adipocytokines such as leptin, adiponectin and proinflammatory cytokines which possess atherogenic effects contributing to adverse metabolic and cardiovascular risk factors [24, 25]. An increase in visceral adiposity is associated with cardiometabolic risk and increased risk of developing coronary heart disease and type 2 DM. Proinflammatory cytokines such as TNF α , IL β and IL 6 and high levels of adipokines secreted from the adipose tissue induces insulin resistance in T2DM [26]. Lipid accumulation in hepatocytes promotes exacerbation in oxidative stress resulting in an inflammatory state through release in IL-6 and monocyte chemotactic protein (MCP-1) [27]. Subsequently, there is an activation of macrophage infiltration, promoting further release of proinflammatory cytokines [28]. The activation of inflammasomes initiates the inflammation. Inflammation causes insulin resistance via inhibiting the signaling downstream of insulin receptor.

Chronic hyperglycemia results in oxidative stress in which there is an excessive production of free radicals. The denoted production of free radicals results in overproduction of proinflammatory cytokines and perpetuated its deleterious effects on pancreatic islets [29]. The proinflammatory cytokines released from the pancreatic β -cells such as IL-1 β , IL-6 and TNF- α and proinflammatory transcription factor, NF- κ B and consequent synthesis of NO radical have been implicated in the pathogenesis and progression of diabetes mellitus. The elevated levels of proinflammatory cytokines (IL-1 β , IL-6 and TNF- α) also potentially induces iNOS and produces NO [30]. NO is highly reactive with superoxide anion forming more toxic peroxynitrite and hydroxyl radicals.

Persistent hyperglycemia mediated oxidative stress leads to the superactivation of stress-sensitive signaling pathways including NF- κ B. The NF- κ B pathway is crucial in regulating inflammatory stress through activation of TNF signaling and toll like receptors to increase the transcription of components of the inflammasomes. The NF- κ B activation is significantly higher in the liver due to obesity and high-fat diet [31]. The levels of pro-inflammatory cytokines such as TNF- α , IL-1 β , and IL-6 were found to be increased in diabetic group of rats. Oral administration of Swertiamarin to HFD-STZ induced diabetic rats decreases the levels of proinflammatory cytokines, NF- κ B, and NO indicating its anti-inflammatory activity and the efficacy was comparable with metformin. This finding suggests that Swertiamarin protects the β -cell integrity by averting inflammatory responses mediated by chronic oxidative stress which might be due to the abolition of ROS and inhibition of NF- κ B and its target genes.

Adipokines are proteins secreted by the adipocytes that are known to have direct or indirect regulation on insulin sensitivity [32]. Leptin and adiponectin ameliorates hyperglycemia in animal models of T2DM [33]. Adiponectin possess an insulin-sensitizing effect. The down regulation of adiponectin leads to insulin resistance resulting in type2 diabetes. Improving adiponectin levels ameliorates insulin resistance which decreases the risk factors of diabetes. The fatty acid oxidation by adiponectin improves insulin sensitivity and facilitates glucose uptake in skeletal muscle. Leptin inhibits appetite, stimulate thermogenesis, decrease the plasma glucose and triglycerides level resulting in reduction in body weight. Chronic hyperglycemia induced leptin resistance results in fat accumulation in type 2 DM. The level of plasma adiponectin is reduced, whereas the concentration of leptin is significantly increased in diabetic rats compared with control rats. The modulation of the pathophysiology of diabetes induced by adiponectin may be due to the increase in glucose uptake mediated by AMPK activation that stimulate phosphorylation of downstream target of AKT, thereby increasing the translocation of the GLUT-4 transporters [34]. However, upon treatment with Swertiamarin, the levels

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of leptin and adiponectin were brought back to normal levels indicating the anti-inflammatory properties of Swertiamarin.

V. CONCLUSION

In conclusion, the results of the present study indicate that Swertiamarin, a major secoiridoid glycoside of *Enicostemma littorale* leaves extract possess significant antidiabetic as well as anti-inflammatory potentials next to its antidiabetic properties.

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