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Original Research Article

Modulating Effect of Vincamine on the Oxidative Stress Markers and Lipid Profile in High Fat Diet and Streptozotocin-Induced Type 2 Diabetic Rats.

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ABSTRACT

Diabetes mellitus, a silent killer and life threatening metabolic syndrome of human population, is not only characterized by hyperglycemia but also with altered status of oxidative stress markers and lipid profile. The study evaluated the modulating effect of vincamine on the oxidative stress markers and lipid profile in high-fat diet and streptozotocin-induced type 2 diabetic rats. Type 2 diabetes mellitus was induced by feeding the animals with a high-fat diet (40%) for 4 weeks followed by a single intraperitoneal dose of streptozotocin (35 mg/kg b.w). Diabetic rats were treated for 30 days with vincamine at a dose of 30 mg/kg b.w orally. Glibenclamide (600 µg/kg b.w) was used as a standard reference drug to compare the antidiabetic activity of vincamine. The status of glucose, insulin, oxidative stress markers, and lipid profile were analyzed to validate the antidiabetic effect of vincamine. Vincamine significantly ($p< 0.05$) reduced the concentrations of blood glucose, glycosylated haemoglobin, total cholesterol, triglyceride, low-density lipoprotein cholesterol, and very-low-density lipoprotein cholesterol and increased the levels of high-density lipoprotein cholesterol and serum insulin. Vincamine administration also decreased thiobarbituric acid reactive substances (TBARS) levels and enhanced the status of catalase, superoxide dismutase, reduced glutathione and glutathione peroxidase. Vincamine has been found to possess antidiabetic, antidyslipidemic, and antioxidant properties and the antidiabetic effect of vincamine was much comparable to that of Glibenclamide, a well knownhypoglycaemic drug. Vincamine thus possesses potential to be used as a natural antidiabetic remedy for the treatment of diabetes mellitus.

Keywords: Vincamine, Streptozotocin, Glibenclamide, High fat diet, Hypoglycemic.

Introduction

Diabetes mellitus is a multifactorial chronic metabolic disorder marked by abnormal levels of blood glucose due to alterations in carbohydrate, protein, and lipid metabolism and is caused by a defect in insulin production, secretion, and function.[1] The annual incidence and prevalence of diabetes mellitus are profoundly increasing in almost all countries. According to the International Diabetes Federation, the number of persons with diabetes in 2017 crossed 425 million,[2]and this number is projected to increase by 25% by the year 2030.[3] It has been suggested that around 50% of the Chinese and Indian population would suffer from diabetes mellitus by the year 2030. Type 2 diabetes is a complex condition that is heavily impacted by environmental variables, the most notable of which is the combination of lifestyle and nutrition. People living with type 2 diabetes are more likely to have microvascular, macrovascular, and acute complications, which can lead to death. The most prominent molecular defect in the onset and evolution of type 2 diabetes is the malfunctioning of the insulin signaling system, which results in insulin resistance when target tissues remain nonresponsive to insulin, leading to glucose uptake failure.[4]

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Type 2 diabetes could lead to excessive generation of reactive oxygen species that can damage many vital organs such as the eyes, nerves, kidneys and blood vessels.[5,6] High levels of reactive oxygen species with a decreased antioxidative defence mechanism, lead to oxidative stress.[7] Decrease in antioxidant defense mechanism causes generations of potent reactive oxygen species which in turn result in abnormal lipid peroxidation in the biological system.[8] Both the lipid profile and diabetes are key predictors of metabolic disorders such as dyslipidemia, hypertension, and cardiovascular disease. Diabetes mellitus is usually accompanied by dyslipidemia, a metabolic disorder.[9] Low high-density level (HDL) cholesterol, a high incidence of tiny dense low-density level (LDL) particles, and high triglyceride levels, all are associated with insulin resistance and type 2 diabetes. Each of these dyslipidemic markers has been associated with a higher risk of cardiovascular disease.Presently, the therapies used for treating diabetes include oral hypoglycemic agents like biguanides, sulphonylureas and thiazolidinediones and insulin injections, which could however possess some drawbacks due to selective mechanism of action.[10] Keeping in view the cost of these synthetic drugs and their adverse effects, interest is growing towards the use of natural products for the treatment of various diseases including diabetes. Phytochemicals open new avenues since they have fewer adverse effects and are less expensive. Several phytochemicals found in medicinal plants, such as alkaloids, flavonoids, terpenoids, and glycosides, act as antioxidants, preventing advanced glycated end products and other diabetes problems linked to oxidative stress.[11] As a result, research into the use of phytochemicals to reduce hyperglycaemia, hyperlipidaemia, and oxidative damage in diabetes mellitus has gained popularity.Vincamine is an indole alkaloid found in the Madagascar periwinkle and is a naturally occurring monoterpenoid.[12] It treats dementia and memory impairments by improving cerebral blood flow, oxygen consumption, and glucose

efficiency.[13] Vincamine is a nootropic healthcare supplement that is commercially supplied in the United States.[14] Diverse biological benefits of vincamine has been reported which include anticancer,[15] antidiabetic,[16,17] nephroprotective,[18] serve as a neuroprotective,[19] antioxidant and anti-inflammatory properties.[20,21] To the best of our knowledge, there are no scientific reports on the antidiabetic effect of vincamine against high-fat diet and streptozotocin-induced diabetes mellitus. The present study thus explores the antidiabetic effect of vincamine in high-fat diet/streptozotocin-induced type 2 diabetic rats.

Materials and Methods

Chemicals
Vincamine was purchased from Sigma-Aldrich (St. Louis, MO, USA), while streptozotocin and other chemicals were obtained from E. Merck HiMedia (Mumbai India). The remaining chemicals and reagents used in the research were of analytical grade.

Experimental animals
Adult healthy male Wistar rats (160-180g) were obtained from Biogen Laboratory Animasl facility, Bengaluru, India, and were maintained in an air conditioned room (25±10°C) with12h/12h cycle (light/dark). They had free access to water as well as a standard pellet diet. Before experimenting, rats were acclimatized to the laboratory environment for 10 days. The study was approved by the ethical committee of Rajah Muthiah medical college **{**Institutional Animal Ethic Committee (IAEC proposal no. Annamalai University-IAEC/1280/10/20)} Annamalai University. The study was carried out as per the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines.

High-fat diet
Experimental rats were divided into groups based on the diet provided (High-fat diet/Normal diet). High fat diet was given for the initial period of 4 weeks after rats were fully acclimatized. HFD composition and preparation [22] are given in (Table 1). After 4 weeks, diabetes was induced in the groups of rats fed with HFD by injecting a single dose of STZ (35 mg/kg i.p) dissolved in a freshly prepared citrate buffer (0.1 M, pH 4.5). The injection volume given to the selected groups was 1ml/animal. After 72 hrs, fasting blood glucose (FBG) concentration was measured and the animals having the fast blood glucose level (FBG) above 250 mg/dL were considered to be diabetic and used for the experiments.

Experimental design
The animals were divided into 4 groups (n=6 each group). Vincamine and glibenclamide were dissolved in 0.5% DMSO and were administered orally to rats (1ml/rat/day) by using oral rat gavage for a period of 30 days.
Group I: Normal control rats
Group II: Rats fed with high HFD (40%) for 4 weeks followed by a single dose of STZ (35 mg/kg b.w) intraperitoneally
Group III: HFD fed-STZ diabetic rats treated with vincamine (30 mg/kg b.w) for 30 days
Group IV: HFD fed -STZ diabetic rats treated with glibenclamide (0.6 mg/kg b.w) for 30 days.

Table 1: Composition of HFD

Ingredients	Standard pellet diet	High-fat diet
Protein	17%	17.7%
Fat+ Beef tallow	4.2% (fat)	35.8 % (Beef tallow)
Carbohydrates	34.5%	34.5%
Fibre	3.4%	3.4%
Minerals	6.8%	6.8%
Vitamins	1.8%	1.8%

Estimation of blood glucose, plasma insulin, haemoglobin, and glycosylated haemoglobin levels
The FBG level was monitored by Glucometer (Accu-Chek Active, Roche, Mannheim, Germany) using the glucose oxidase method.[23] The plasma insulin was evaluated by using enzyme linked immunosorbent assay (ELISA) using Boehringer Mannheim kit (Boehringer analyzer ES300).[24]Haemoglobin in the blood was estimated by the method of Drabkin and Austin.[25] The glycosylated haemoglobin (HbA1c) was estimated by the method of Bannon.[26]

Estimation of serum lipid profile
Triglyceride (TG), total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-C) concentrations in the serum were evaluated using commercially available kits from SwemedBiomedicals, Pvt ltd., Bengaluru, India. Friedewald's formula, (LDL = (TC-HDL)-TG/5 and VLDL cholesterol = TG/5) has been used to calculate low-density lipoprotein cholesterol (LDL-C) and very-low-density lipoprotein cholesterol (VLDL-C).[27] The Zilversmit and Davis methodology was used to estimate the phospholipids in serum.[28]

Estimation of oxidative stress markers in plasma, liver and kidney
The activity of superoxide dismutase (SOD) was analyzed by using the method of Kakkar*et al*.[29] TBARS was measured in plasma by the method of Yagi[30] and in tissues by the method of Ohkawa*et al*.[31] CAT activity was determined by the method of Sinha.[32] The activity of Glutathione peroxidase (GPx) was determined by the method of Rotruck*et al*.[33] The activity of reduced GSH was assayed by the method of Ellman.[34]

Statistical analysis
All the results were expressed as mean±SD (standard deviation). The statistical comparison was done by one-way analysis of variance (ANOVA) followed by Duncan's multiple range test (DMRT) using the SPSS software package. The results were considered statistically significant if p values were less than 0.05.

Results and Discussion

Effect of vincamine on fasting blood glucose, plasma insulin, haemoglobin, and glycosylated haemoglobin
The effect of vincamine on variations in FBG level is shown in Table 2. When compared to control rats, the FBG level in HFD/STZ diabetic rats was considerably higher. A marked decline in total Hb and an elevation in HbA1c levels was found in diabetic rats. However, the administration of vincamine (30 mg/kg b.w) restored the blood glucose, insulin and haemoglobin status in diabetic rats. The antidiabetic effect of vincamine was found to be comparable to that of the reference drug, glibenclamide.
Diabetes mellitus, a metabolic syndrome, has been reported to cause significant morbidity and mortality in human populations and is recognized as a silent killer of the human population.[35] Type 2 diabetes is a long-term metabolic condition marked by hyperglycaemia, dyslipidaemia, and insulin resistance. Several studies have found that combining HFD with a low dose of STZ causes hyperglycaemia, resistance to insulin, and insulin insufficiency. According to previous studies, HFD feeding rats can accelerate the progression of insulin resistance in an animal experimental paradigm.[36]. High doses of STZ injections have been reported to severely impair pancreatic cell function, resulting in defects in insulin secretion, which mimics Type 1 diabetes mellitus. The combination of HFD with low-dose STZ injections has recently been shown to impair β-cell function and cause a slight loss of insulin secretion, which is analogous to the intuitive pathogenesis of human type 2 diabetes mellitus.[37]. Forthese reasons, in the current investigation, Wistar rats were given an HFD for 4 weeks followed by a low dose of STZ (35 mg/kg b.w) to induce type 2 diabetes mellitus as well as to study the antidiabetic effect of vincamine.The combination of HFD and modest doses of STZ led to type 2 diabetes mellitus, in which insulin resistance figures prominently in pathophysiology, leading to different metabolic disorders such as chronic hyperglycaemia, hyperinsulinemia, and dyslipidaemia.

The study noticed an elevation in the blood glucose level, which was accompanied by decreased plasma insulin and increased glycosylated hemoglobin in diabetic rats. Decreased total hemoglobin and increase in blood glucose might have been responsible for the observed increase in HbA1c in diabetic rats.[38] Vincamine administration restored the status of blood glucose, insulin, and hemoglobin levels in diabetic rats which implies that vincamine can stimulate the secretion of insulin from surviving/undamaged pancreatic β cells. The antidiabetic effect of vincamine might be due to its ability to promote glucose utilization by the peripheral tissues of diabetic animals.[39]Theantidiabetic effect of vincamine was also found to be comparable to that of glibenclamide.

Effect of vincamine on oxidative stress markers in plasma, liver, and kidney

Table 3-5 shows that the diabetic control group has a significant rise in TBARS levels and a significant decrease in SOD, CAT, GSH, and GPxactivities in plasma, liver, and kidney.Vincamine-treated diabetic rats showed decreased levels of TBARS and increased levels of SOD, CAT, GSH, and GPx as compared to diabetic rats. The results observed in the vincamine-treated diabetic rats are comparable to that of glibenclamide.

STZ is commonly employed to induce diabetes mellitus as STZ has been able to cause pancreatic *β*-cells damage by giving rise to excessive reactive oxygen species (ROS).[40] It has been demonstrated that STZ caused DNA breaks as well as produced abundant reactive oxygen species in the pancreatic islet cells. Profound human and experimental studies have also reported abnormal lipid peroxidation dragged by the disturbed antioxidant cascade in the circulation(human diabetic population) and both circulation and tissues of experimental diabetic animals.[41] Several authors documented an elevated TBARS level and downturn of enzymatic and non-enzymatic status in HFD/STZ induced diabetic rats.[42-44] The present study observed an increase in the level of TBARS with decreased activities of antioxidants in the plasma, liver, and kidney of diabetic rats as compared to control animals.

Table 2: Status of fasting blood glucose, plasma insulin, Hb, and glycosylated haemoglobin in control and experimental rats

Groups	FBG (mg/dL)	Plasma Insulin (µU/mL)	Hb (mg/dL)	HbA1c (%)
Control	88.74 ± 7.19^{c}	17.45 ± 3.63^{b}	12.62 ± 1.48^{b}	6.05 ± 0.39^{c}
Diabetic (HFD+STZ)	309.28 ± 22.37^{a}	9.06 ± 2.60^{c}	6.75 ± 1.77^{c}	10.93 ± 0.69^{a}
Diabetic+Vincamine	107.58 ± 9.22^{b}	14.89 ± 3.51^{b}	10.88 ± 1.61^{b}	8.63 ± 0.80^{b}
Diabetic+glibenclamide	105.46 ± 6.06^{b}	16.03 ± 2.88^{b}	12.02 ± 1.89^{b}	7.02 ± 0.59^{b}

All the results are expressed as mean ± SD (n=6). Mean values that are not sharing a common superscript in the given column are significantly different (P≤0.05) as judged by DMRT.

Table 3: Status of oxidative stress markers in the plasma of control and experimental rats

Groups	SOD (U/mL)	TBARS (nmol/mL)	CAT (U/mL)	GSH (µmol/L)	GPx (U/L)
Control	8.62 ± 0.39^{a}	0.28 ± 0.06^{c}	171.27 ± 7.79^{a}	33.52 ± 5.41^{a}	17.93 ± 1.98^{a}
Diabetic (HFD+STZ)	4.12 ± 0.49^{c}	0.72 ± 0.15^{a}	102.27 ± 3.34^{b}	17.16 ± 2.59^{c}	8.54 ± 0.99^{c}
Diabetic + vincamine	6.02 ± 0.36^{b}	0.36 ± 0.16^{b}	160.06 ± 15.95^{a}	27.47 ± 2.68^{b}	14.94 ± 1.00^{b}
Diabetic + glibenclamide	7.37 ± 0.25^{b}	0.32 ± 0.14^{b}	166.16 ± 13.07^{a}	29.09 ± 3.35^{ab}	15.63 ± 0.91^{b}

All the results are expressed as mean ± SD (n=6). Mean values that are not sharing a common superscript in the given column are significantly different (P≤0.05) as judged by DMRT.

Table 4: Status of oxidative stress markers in the liver of control and experimental rats

Groups	SOD (U/mg protein)	TBARS (mmol/mg protein)	CAT (U/mg protein)	GSH (U/mg protein)	GPx (nmol/min/mg protein)
Control	21.97 ± 0.32^{a}	1.05 ± 0.20^{c}	80.02 ± 4.3^{a}	15.85 ± 2.4^{a}	12.95 ± 0.87^{a}
Diabetic (HFD+STZ)	8.02 ± 0.27^{c}	4.86 ± 0.26^{a}	52.09 ± 3.0^{c}	7.14 ± 2.8^{c}	4.80 ± 3.6^{d}
Diabetic + vincamine	18.67 ± 0.60^{b}	1.85 ± 0.26^{b}	73.29 ± 3.2^{b}	10.78 ± 2.3^{b}	7.88 ± 0.59^{c}
Diabetic + glibenclamide	21.35 ± 0.21^{ab}	$1.91 \pm 0.0.28^{b}$	76.08 ± 9.6^{b}	13.10 ± 0.87^{b}	9.28 ± 0.65^{b}

All the results are expressed as mean ± SD (n=6). Mean values that are not sharing a common superscript in the given column are significantly different (P≤0.05) as judged by DMRT.

Table 5: Status of oxidative stress markers in the kidney of control and experimental rats

Groups	SOD (U/mg protein)	TBARS (mmol/mg protein)	CAT (U/mg protein)	GSH (U/mg protein)	GPx (nmol/min/mgprotein)
Control	19.02 ± 2.8^{a}	1.29 ± 0.37^{b}	55.70 ± 4.9^{a}	13.24 ± 0.69^{a}	9.02 ± 0.56^{a}
Diabetic (HFD+STZ)	10.03 ± 4.1^{c}	3.89 ± 0.67^{a}	32.98 ± 2.2^{c}	7.24 ± 0.79^{c}	4.94 ± 0.76^{c}
Diabetic+ vincamine	14.92 ± 4.8^{b}	1.73 ± 0.38^{b}	48.91 ± 2.9^{b}	10.87 ± 0.71^{b}	6.50 ± 0.72^{b}
Diabetic+ glibenclamide	16.23 ± 4.0^{b}	1.55 ± 0.54^{b}	51.05 ± 5.3^{b}	11.19 ± 0.91^{b}	8.04 ± 0.66^{b}

All the results are expressed as mean ± SD (n=6). Mean values that are not sharing a common superscript in the given column are significantly different (P≤0.05) as judged by DMRT.

Vincamine administration (30 mg/kg b.w orally) to diabetic rats retrieved the status of TBARS and antioxidants to the near-normal range.It is well known that hyperglycaemia is one of the pathological consequences able to generate excessive reactive oxygen species in the body. Over production of reactive oxygen species due to hyperglycaemia affects the membrane integrity and leads to excessive lipid peroxidation in the membrane.[45] High levels of TBARS were also reported in the liver and kidneys of diabetic animals.[46] The measurement of TBARS in the plasma may assist to know the severity of the tissue damage, increased plasma TBARS observed in the present study could be due to its excessive generation in the liver and kidney with a subsequent leakage in the plasma.[47] Accumulated evidence from the studies on diabetes mellitus pointed out an inverse association between the status of oxidants and antioxidants. An increase in plasma TBARS could be due to defective antioxidant defence mechanisms in diabetic animals.[48] It has been reported that STZ induced hyperglycaemia stimulated excessive generation of reactive oxygen species, which could able to cause extensive oxidative damage in the tissues.[49]

SOD, CAT, GSH are biologically important endogenous antioxidants that form the first line of defence mechanism against ROS-mediated tissue damage.[50] Decreased activities of SOD and CAT suggest that diabetic animals are prone to more oxidative stress. Decreased glutathione content in the blood affect tissues of diabetic animals could reveal its stimulation circulation to counteract the effect of excessive generated reactive oxygen species during diabetes mellitus.[51,52]Vincamine administration to the diabetic animals not only retrieved the status of blood glucose but also ameliorated the hyperglycemia-induced oxidative stress in diabetic animals. The present study thus suggests that vincamine has a potent glycemic control mechanism and could be recommended as a candidate for the treatment of diabetes mellitus.

Effect of vincamine on serum lipid profile

The effect of vincamine on the serum lipid profile is shown in Table 6. Serum triglycerides, total cholesterol, LDL-C, and VLDL-C levels were significantly higher in the diabetic group as compared to the control group, whereas HDL-C levels were found to be significantly lower. Oral administration of glibenclamide (0.6mg/kg b.w.) and vincamine (30 mg/kg b.w.) to diabetic rats resulted in a considerable reduction in TC, TG, LDL-C, and VLDL-C levels and an increase in the HDL-C levels.

Lipids play a pivotal role in determining the structure and functions of the cell membrane. Abnormalities in lipids could lead to several complications. Most of the diabetic subjects are reported to have hyperlipidaemia as well as dyslipidaemia complications. Accumulation of cholesterol, TG, phospholipids, and decreased levels of HDL-C has been well documented in diabetes and its complications.[53,54] Several studies pointed out the correlation between obesity and diabetes. Human [55,56]and experimental studies [57,58] has also shown abnormal lipid pattern in the plasma and serum. It has been pointed out that impairment in insulin sensitivity occurring in diabetes mellitus due to abnormal levels of lipids could be responsible for cardiovascular risk in patients with diabetes mellitus. Accumulated evidence has documented altered pattern of plasma lipids and lipoprotein patients with type 1 and type 2 diabetes mellitus. Thus, to improve the glycaemic control mechanism in the diabetic population the treatment of dyslipidaemia could also be essential in addition to treating hyperglycaemia.

In the present study, we observed increased levels of cholesterol, phospholipids, triglycerides, LDL-C and decreased levels of HDL-C in the plasma of HFD/STZ induced diabetic rats. The investigation on the status of plasma lipids in diabetic patients could help to assess the development of cardiovascular diseases and atherosclerosis in diabetic subjects. The onset of atherosclerosis in diabetic patients has been associated with abnormal plasma TG levels accompanied by a reduction in plasma HDL- C levels.[59,60] The administration of vincamine to HFD/STZ diabetic rats dropped cholesterol, phospholipids, triglycerides, and LDL-Clevels while raising HDL-C levels.

The results of the present study thus indicate that vincamine has not only improved the glycaemic control mechanism in diabetic rats but also corrected the abnormalities noticed in the plasma lipids pattern in HFD/STZ induced diabetic rats. The current investigation thus concludes that vincamine has potent antihyperglycemic and antihyperlipidemic effects in HFD/STZ induced diabetic rats and thus vincamine can be considered as a potent candidature for the treatment of diabetes mellitus.

Table 6: Status of Serum Lipid profile in control and experimental rats

Groups	Control	Diabetic (HFD + STZ)	Diabetic + Vincamine	Diabetic + Glibenclimide
TC (mg/dL)	94.59 ± 10.4^{c}	164.43 ± 19.1^{a}	108.77 ± 11.09^{b}	105.61 ± 10.84^{b}
TG (mg/dL)	78.54 ± 3.51^{c}	160.02 ± 5.45^{a}	87.97 ± 2.06^{b}	84.94 ± 1.53^{b}
HDL (mg/dL)	42.51 ± 4.50^{a}	19.97 ± 2.63^{c}	27.94 ± 3.22^{b}	30.50 ± 4.53^{b}
LDL (mg/dL)	36.37 ± 4.05^{c}	112.45 ± 2.45^{a}	61.63 ± 11.86^{b}	58.11 ± 8.91^{b}
VLDL (mg/dL)	15.72 ± 0.73^{c}	32.00 ± 1.09^{a}	19.18 ± 0.41^{b}	16.98 ± 0.30^{b}
Phospholipids (mg/dL)	116.13 ± 5.37^{c}	153.94 ± 13.83^{a}	128.06 ± 10.15^{b}	123.43 ± 10.27^{b}

All the results are expressed as mean ± SD (n=6). Mean values that are not sharing a common superscript in the given roware significantly different ($P \leq 0.05$) as judged by DMRT.

Conclusion

In addition to the antihyperglycemic effect, vincamine reduced the lipid profile of diabetic animals significantly. Vincamine also decreased oxidative stress-related metabolic complications. The positive impact on lipid profile and improvement in oxidative stress parameter were comparable to that of glibenclamide, indicating that vincamine has a potent anti-diabetic property.

Conflict of Interest

The authors declare no conflict of interest.

Authors Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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