



Evaluation of the Antihyperlipidemic and Antioxidant Effects of *Catharanthus roseus* Extracted from *Vinca minor* in Diabetic Rats

Shimaa Mohammed Hasnin Aboelnaga^{1*}

¹*Deanship of Preparatory Year, University of Ha'il, Kingdom of Saudi Arabia.*

Author's contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

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ABSTRACT

The role of oxidative stress is known among the patients of diabetes as the level of reactive oxygen species was high among diabetic patients. This oxidative stress is generated in diabetic patients due to continuous high glucose levels that cause to decrease in the defence mechanism for antioxidant enzymes within the body. The reduction of the antioxidant defence mechanism leads towards the generation of hydroxyl radicals consequently results in lipid peroxidation. The objective of this study is to examine the efficacy of Vincamine extracts as antihyperlipidemic and antioxidant in diabetic rats. To evaluate the antihyperlipidemic and antioxidant effects of Vincamine, adult BB Wistar rats, weighing 150- 170 g were obtained and divided in six groups. Blood analysis was taken measure the observed parameters. The findings showed vincamine display antioxidant, hypoglycaemic and hypolipidemic activity. It is concluded that vincamine has a protective role and acts as a good antioxidant activity along with effective antidiabetic effects.

Keywords: *Diabetes Miletus (DM); vincamine extracts; Catharanthus roseus; Streptozotocin (STZ).*

*Corresponding author: E-mail: shimaasmart@yahoo.com;

1. INTRODUCTION

Diabetes Mellitus (DM) is one of the chronic metabolic disorders that are caused due to alterations in the levels of glucose within the body [1]. The disturbance or alteration in the production and action of insulin results in the development of signs and symptoms of diabetes mellitus. It is observed that in the case of DM, there are several issues associated with the carbohydrates, protein, and lipids contents in the body. According to the statistics of the United States, there are about 34.2 million Americans are involved in the disease of diabetes. Out of which 1.6 million are involved in type 1 diabetes [2]. Besides, there were about 7.3 million cases undiagnosed with diabetes. This was also observed that a high rate of diabetes is among individuals with old age. Furthermore, about 1.6 million cases of diabetes report every year [3].

The decrease of the antioxidant defence mechanism affects the generation of hydroxyl radicals results in lipid peroxidation. This is caused by the pancreas has beta cells that are more susceptible to oxidative damage [4]. There is necessary action to maintain stable glucose concentrations in the blood to prevent the occurrence of diabetes among the patients. There are many medicines used for the treatment of diabetes. However, this has been noticed that there is no effective treatment therapy available for the complete cure of diabetes. Certain therapies and treatments are found costly also with fewer efficacies among diabetic patients [5]. Due to the higher cost of the treatment and therapies, people from low socioeconomic status often cannot afford these treatments. The lack of accessibility to effective treatment is a major factor that reduces the rate of morbidity and mortality among diabetic patients [6].

It is observed in recent years that there is an increased demand for the utilisation of natural products for the treatment of diabetes. These natural products are found to be more effective with no or minimal side effects among diabetic patients. The application of extracts from the plants is also found effective for the treatment of diabetes. Researchers and scientists are doing researches to explore the use of effective extracts from plants for the reduction and prevention of high blood glucose levels and indicated that the use of an alkaloid named Vincamine was found effective in diabetes care and management [7]. Vincamine is an alkaloid found in plants with the Latin name *Catharanthus*

roseus. This plant is also known to have anti-cancer properties. Overall, it was found that the use of plant extracts is efficacious for the control of diabetes [8].

There are several phytochemicals such as vincristine and vinblastine extracted from the plants. These phytochemicals are found effective for activities such as antioxidant, antimicrobial, and antidiarrheal and also for antidiabetic activities [9]. Besides, this was also found that vincamine also exhibits antioxidant and antihyperlipidemic activities. This is also used to treat cancer among children. The mechanism of the activities is not known yet. There is a need for further research studies to study the mechanism of action in detail. However, the effects include the reduction in the formation of free radicals within the body resulted in strong antioxidant activities. Besides, there is less deposition of glycerol contents in the body due to the action of these phytochemicals. The efficacy of this compound for the treatment of diabetes has been analysed through experimenting with diabetic rats. In the previous studies, there are advantages reported about the use of Vincamine such as an increase in memory, blood thinning, etc. Based on the above information, the following were the research objectives of this study. 1). To examine the antidiabetic effects of Vincamine in diabetic rats. To explore the antioxidant and antihyperlipidemic properties of Vincamine using the diabetes rat model. The research questions of the study were; 1). What are the effects of Vincamine on the glucose level of diabetic rats? 2). What will be the effects of antioxidant and antihyperlipidemic properties of Vincamine in diabetic rats.

2. METHODS

2.1 Data Collection

The current qualitative research has collected secondary data to investigate the antioxidant and antihyperlipidemic effects of Vincamine in diabetic rats. Secondary sources including, published research papers, journal articles, and eBooks have been used to extract relevant data and information related to the experiments carried out by previous researchers on diabetic rats for assessing the impacts of Vincamine in them. The articles incorporated in this study have been retrieved via specific online databases including, PubMed, Science Direct and Embase. In addition to this, relevant keywords were used to retrieve secondary sources which

include, 'antioxidant', 'antihyperlipidemic', 'Vincamine', 'diabetes', 'rats', 'hypolipidemic agents', 'Bio-Breeding (BB) rats', 'Wistar rats', 'effects', 'impact', 'hypoglycemia' etc.

For the selection and integration of relevant articles, the current study has also outlined an inclusion and exclusion criteria, which has assisted in incorporating relevant information while, excluding irrelevant content. The inclusion and exclusion criteria set in this study is given below.

1. The studies which have extensively focused on the properties of Vincamine extracted from plant *Vinca minor*, in diabetic rats were included.
2. The articles integrated in this study have used Bio-Breeding (BB) Wistar rats weigh between 150-170g.
3. Besides, the studies that emphasized on the antioxidant and antihyperlipidemic effects of Vincamine have been included in this study.

2.2 Materials and Methods

Certain important materials and techniques that have been used in the selected article, proposed by Nandini and Naik (2019), to conduct an experiment in rats are discussed as follows;

2.2.1 Chemicals

For this experiment, Vincamine was required, which is a vinca alkaloid ester, an organic heteropentacyclic compound, and plays significant role as a vasodilator agents, a metabolite, and antihypertensive agent. Other than this, commercial diagnostic kits were also bought, to estimate biochemical parameters. Along with these materials, some other chemicals were acquired from standard commercial chemical suppliers and used for analytical grading in the experiment.

2.2.2 Experimental animals

To evaluate the antihyperlipidemic and antioxidant effects of Vincamine, adult BB Wistar rats, weighing 150- 170g were obtained and preserved in a room at an air-conditioned temperature i.e. $26 \pm 10^\circ\text{C}$, with a 12 hours dark and 12 hours light cycle. A standard pellet diet along with water ad libitum were provided to preserved rats, to prevent them from any morbidities or fatalities.

2.2.3 Induction of experimental diabetes

Diabetes has been induced by injecting 40 mg/kg streptozotocin in 12 h fasted rats. The streptozotocin was dissolved in a freshly prepared citrate buffer with pH 4.5 and 1 ml has been injected intraperitoneally in a rat. After 72 hours of induction, the rats with fasting blood glucose level more than 235 mg/dl have been classified as diabetic and included in the experiment.

2.2.4 Experimental design

The rats included in the experiment have been divided into six groups and acquired treatment enlisted as follows:

Group I: Control

Group II: Disease control rats (STZ)

Group III: Vehicle Control (0.5% Dimethyl sulfoxide (DMSO))

Group IV: Diabetic + Vincamine (30 mg/kg body weight/day)

Group V: Diabetic + Glibenclamide (0.1 mg/kg body weight/day)

Group VI: Diabetic + Vincamine (20 mg/kg body weight/day)

These treatments have been provided to rats via oral administration for a period of thirty days and rat gavage was used for appropriate administration. During the last treatment, under mild ether anaesthesia rats were autopsied, as well as, fasted overnight. However, blood from their carotid artery was drawn and centrifuged to be used for the analyses of biochemical.

3. FINDINGS

3.1 Vincamine Effects on Diabetic Rats' Serum Lipid Profile

The current study has taken into consideration the findings of a research proposed by Nandini and Naik (2019), in which 12 h fasted rats were injected 40mg/kg streptozotocin, in order to, induce diabetes into them. However, the rats with fasting blood glucose concentration above 235 mg/dl had been used in this study to observe the effects of Vincamine. Other than this, standard kits were used, in this experiment, to determine

the serum concentrations of triglyceride, high-density lipoprotein cholesterol (HDL-C), and total cholesterol of the rats while, Friedewald's formula was used to calculate low-density lipoprotein cholesterol (LDL-C) and very low-density lipoprotein cholesterol (VLDL-C). The findings depicted that the serum concentration of LDL-C, VLDL-C, triglyceride, and total cholesterol have significantly increased in rats which were placed in diabetic group i.e. $96.22 \pm 1.91d$, $31.24 \pm 0.13e$, $157.03 \pm 1.70d$ and $156.17 \pm 0.63e$, respectively in comparison to those in the control group. In contrast, the HDL-C in diabetic rats has significantly decreased, $29.57 \pm 0.44a$, as observed in following Table 1.

Furthermore, Table 1 shows that the Vincamine, extracted from the plant *Vinca minor*, 20 mg/kg.bw and glibenclamide 30 mg/kg.bw were orally administered into rats and a significant decrease was reported in the serum concentration of LDL-C, VLDL-C, triglyceride, and total cholesterol. On the contrary to diabetic rats, the level of HDL-C in control group, after the administration of Vincamine and glibenclamide, was observed to have markedly increased. In addition to this, it was found in the study that, the 30mg/kg.bw (mg/kg per body weight per day) of Vincamine extracts could have more effective impact on lipid profile, in comparison to 20 mg/kg.bw Vincamine extracts.

3.2 Vincamine Effects on Body Weight, Plasma Insulin, Fasting Blood Glucose, and Glycosylated hemoglobin of STZ-Diabetic Rats

It has been observed in a study that, prior to the analysis of the effects of Vincamine in rats, their fasting blood glucose levels were determined via glucometer at weekly interval. Glucose oxidase method was used to monitor the fasting blood glucose. In addition to this, the glycosylated hemoglobin (HbA1c) was monitored via standard measuring kit. The findings have been shown in the following Fig. 1.

Furthermore, the plasma insulin of rats was determined by using specified insulin kit. As a result, it was found that the fasting blood glucose level of streptozotocin-induced diabetic rats has significantly increased comparatively to those rats placed in the control group. Besides, doses of Vincamine extracts, at 20 mg/kg.bw and 30 mg/kg.bw were orally administered and a marked decrease in the glucose level of STZ-induced diabetic rats has been observed. Similar results

were observed in rats that were given a 0.1 mg/kg.bw dose of glibenclamide, as shown in Fig. 2.

On the other hand, a considerable reduction in the plasma insulin, as well as, body weight of diabetic control rats. However, when rats treated with 20 and 30 mg/kg Vincamine extracts and glibenclamide, their levels of plasma insulin, along with body weight were restored to optimal level as observed in Table 2.

Table 2, shows the mean \pm SD for each group when rats treated with 20 and 30 mg/kg Vincamine extracts and glibenclamide i.e., Control ($222.00 \pm 2.96b$), Vehicle Control (0.5% DMSO) ($211.00 \pm 4.33b$), Diabetic Control ($146.40 \pm 1.72a$), Diabetic+Glibenclamide (0.1mg/kg body weight/day) ($213.80 \pm 6.58b$), Diabetic+Vincamine (20 mg/kg body weight/day) ($220.40 \pm 1.50b$), and Diabetic+Vincamine (30 mg/kg body weight/day) ($218.40 \pm 3.32b$).

3.3 Vincamine Effects on Antioxidant Activities of Diabetic Rats

Proceeding with this process, the antioxidant activities of rats were assessed, so as to, clearly interpret significant differences. At 406 nm of SOD, the superoxide driven oxidation of quercetin was observed to have inhibited in the assay. Moreover, the mixture was found to have 0.8 mM TEMED, enzyme that inhibits quercetin autooxidation by 50%, 25 mM phosphate buffer and 0.25Mm EDTA.

Additionally, the catalase activity was also assessed, followed by the clearance of H₂O₂, in a reaction mixture, at 240 nm. Besides, the reaction mixture consisted of 0.012% TRITONX100, 50 mM phosphate buffer, 10 mM H₂O₂ and 0.5 mM EDTA. Lastly, the final volume of samples, placed in 96-well microtiter plates, was made up to 100 μ l, by adding 25 μ l Ophthalaldehyde, and 100 mM phosphate buffer. The final sample was then placed in an incubator at 37°C for 45 mins.

The findings have shown a significant decrease in the catalase activity, SOD and glutathione activities in the kidney and liver of diabetic rats, in comparison to those placed in control group. On the other hand, rats treated with 20 and 30 mg/kg Vincamine extracts and glibenclamide were observed to have shown a significantly increased levels of glutathione level, activities of SOD and catalase activity, in comparison to diabetes-induced rats (Nandini and Naik, 2019) (See Appendix 1).

Table 1. Effects of vincamine on diabetic rats' serum lipid profile

Groups	Total cholesterol mg/dL	Triglycerides mg/dL	HDL cholesterol mg/dL	LDL cholesterol mg/dL	VLDL cholesterol mg/dL
Control	90.38±1.22 ^a	72.34±1.23 ^a	54.34±0.40 ^c	21.57±1.59 ^a	14.47±0.25 ^a
Vehicle control (0.5% DMSO)	92.92±0.92 ^a	73.97±0.71 ^{ab}	53.73±0.78 ^c	24.39±1.19 ^a	14.79±0.14 ^{ab}
Diabetic control	157.03±1.70 ^d	156.17±0.63 ^e	29.57±0.44 ^a	96.22±1.91 ^d	31.24±0.13 ^e
Diabetic + Glibenclamide (01 mg/kg body weight/day)	93.63±1.19 ^{ab}	75.60±1.29 ^{bc}	47.65±1.46 ^b	30.86±1.79 ^b	15.12±0.26 ^{bc}
Diabetic + Vincamine (20 mg/kg body weight/day)	102.26±1.22 ^c	80.18±0.96 ^d	44.10±1.39 ^b	42.12±2.07 ^c	16.04±0.19 ^d
Diabetic + Vincamine (30 mg/kg body weight/day)	97±0.77 ^b	77.34±0.85 ^{cd}	46.16±1.89 ^b	35.37±2.08 ^b	15.47±0.17 ^{cd}

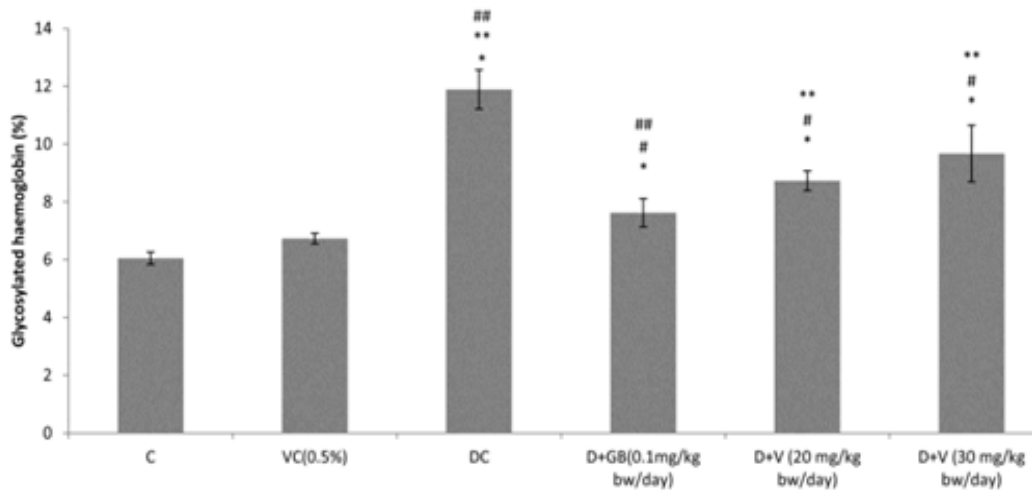


Fig. 1. Effect of vincamine on glycosylated haemoglobin in streptozotocin-induced diabetic rats. C, control; VC, vehicle control; DC, diabetic control; D, diabetic; GB, glibenclamide; V, vincamine

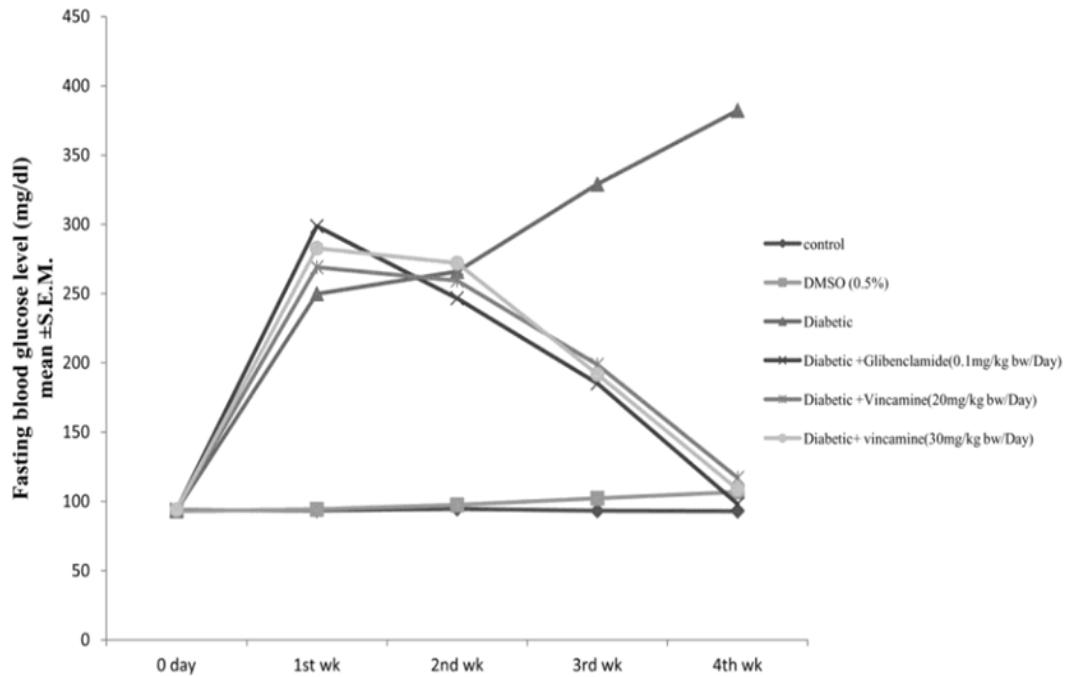


Fig. 2. Effect of vincamine on fasting blood glucose concentration at weekly intervals (4 weeks) in streptozotocin-induced diabetic rats

Table 2. Effect of Vincamine on Body Weight of Rats

Groups	Body weight (g)	
	Initial	Final
Control	181.00±0.89	222.00±2.96 ^b
Vehicle control (0.5% DMSO)	178.80±2.41	211.00±4.33 ^b
Diabetic control	185.20±1.15	146.40±1.72 ^a
Diabetic + Glibenclamide (01 mg/kg body weight/day)	178.00±3.42	213.80±6.58 ^b
Diabetic + Vincamine (20 mg/kg body weight/day)	185.60±1.07	220.40±1.50 ^b
Diabetic + Vincamine (30 mg/kg body weight/day)	186.80±1.74	218.40±3.32 ^b

4. DISCUSSION

Diabetes Miletus (DM) is one of the major concerns nowadays due to its high incidence and the prevalence rate throughout the world [10]. The present study was conducted to check the effects of vincamine on diabetic rats. According to the findings of the present study, it was found that vincamine displayed a protective role and provides good antioxidant activities along with effective antidiabetic effects. In comparison with the previous studies, it was found that vincamine has several pharmacological advantages such as this cause to impact the antioxidant defense mechanism along with the antidiabetic effects [11]. This was documented that vincamine is also used in the United States and Europe for the treatment of degeneration and dementia. The study also showed the efficacy of vincamine for the cure of tinnitus. The study showed the findings in agreement with the present study that vincamine showed a significant decrease in fasting blood glucose levels towards normal [12]. Vincamine may result in an increase in glucose utilisation due to the enhanced uptake of peripheral glucose [13].

However, in another study, it was found that vincamine can also be used for the treatment of hypertension. The pharmacological application of this plant extract has been known for the problems in the central nervous system as well as the cardiovascular system [14]. This was also observed that the vincamine has antidiabetic effects. Therefore, the present study was carried out to find out the antioxidant, antihyperlipidemic along with antidiabetic effects of the vincamine. The findings of the study showed that the vincamine exhibits therapeutic effects such as antioxidant, antidiabetic, and antihyperlipidemic. The study used the methods of secondary data collection in which the results were obtained by using the previous research studies carried out to

examine the effects of vincamine. The previous studies employed the streptozotocin to induce diabetes in the rats. This was observed in the studies that the induction of diabetes using streptozotocin cause to decrease in the body weight due to damage to the structural proteins. This damage to the proteins was due to the improper availability or deficiency of carbohydrates [15]. The breakdown of lipid and protein molecules affects the bodyweight of diabetic rats. Therefore, it was noticed that the reduced bodyweight of the diabetic rats was due to the induction of streptozotocin in the rats. A study showed that there was an increase in the body weight in diabetic rats after the rats were exposed to the vincamine. This showed that there were positive impacts of using the vincamine on the diabetic rats and there was no degradation of the proteins in the case of exposure to this plant extracted compound [16].

The study indicated that hyperglycaemia (increased concentration of the glucose levels in the blood) is the condition caused due to the increased activity of gluconeogenesis within the body. This can be occurred in the body due to the decrease of insulin secretion that will be because of the breakdown of beta cells of the pancreas [17]. The findings of the present study indicated that the use of vincamine affects the levels of decreased blood glucose levels positively and leads towards the normal levels in the blood. This phenomenon can be caused due to the increase of glucose uptake within the body by biochemical actions. The study showed that the normalisation of the blood glucose levels due to the use of vincamine can be due to the improvement in the insulin levels of the blood. The mechanism involved in the increase of the insulin activity of the blood can be due to the enhancement in the insulin release from the beta cells of the pancreas [18]. The studies also reported the therapeutic activities such as

antidiabetic effects of several other alkaloids. The level of HbA1c indicates the amount of hemoglobin attached to the level of glucose [19]. This was found that the amount of HbA1c enhances with the reduction of hemoglobin levels. This was due to the increased amount of glucose within the blood that forms the reaction with the haemoglobin.

The study showed that the vincamine reduced the HbA1c in diabetic rats. The reason for this activity was due to the decrease in blood glucose levels. The same results have been found in other studies that showed the effectiveness of using phytochemicals for the improvement of antioxidant defence mechanisms [20]. This was observed in the previous studies that in the case of diabetes, high glucose levels are usually associated with dyslipidaemia that increase the risk of stroke or cardiac diseases. The findings of the present study indicated that in the serum samples of the diabetic rats, there is an increased amount of fats found. This also caused to enhance the transformation of fatty acids into cholesterol or phospholipids. The increase of the lipoproteins in the blood samples of the rats was found in the diabetic rats. The data collected also showed that the cure and treatment of diabetes involved the level of glucose along with the lipid contents in the plasma [21].

The prevalence of diabetes in diabetic rats occurred due to the higher levels of glucose that also cause an increase in the glycerides' contents and cholesterol levels. The problems in the regulation of insulin activity also damage the normal functioning of the breakdown of lipids and fatty acid contents in the plasma. The diabetic issue was also found to be related to the condition of high cholesterol and lipid contents in the plasma. The increase of the cholesterol contents occurred due to the enhancement in the biosynthesis of the cholesterol contents and the reduction of absorption of the cholesterol contents [22].

The findings of the study showed that the use of vincamine extracts also affects significantly the reduction of cholesterol contents in diabetic rats. Besides, this was also noticed that diabetes affects the antioxidant defence mechanism within the body and increased the complications due to the increased stress of oxidative enzymes [23]. The increase of the glucose levels also increases the production of reactive oxygen species. The use of phytochemicals was also found effective in reducing oxidative stress and control of the

generation of hydroxyl radicals, hydrogen peroxides, and superoxide ions. This was suggested to use the extracts of plants for the control of blood glucose levels along with oxidative stress. The superoxide radical is also found to be associated with harm to the cell membranes and the structure of the biological molecules [24].

The activity of antioxidant enzymes was found to be increased with the increase of diabetes in rats. The use of vincamine was found effective in the study to strengthen the activities of antioxidant activities in diabetic rats. The findings indicated that the use of vincamine is effective for the control of the level of diabetes and reduce the lipids and cholesterol contents in the diabetic rats. The use of vincamine was also found effective in the control of the generation of the reactive oxygen species. The findings of the study were supported by previous studies [25].

5. CONCLUSION

The findings of the study indicated that the use of vincamine is effective in the control of diabetes as well as exerts positive impacts on the activities of antioxidant enzymes. Besides, the levels of lipids and cholesterol can also be maintained and regulated in the blood by the use of vincamine. Therefore, it is concluded that the use of vincamine is effective in the control of diabetes along with the complications that can be caused in diabetic rats. Future studies are required to do detailed work on the cellular and molecular level to find out the effectiveness of vincamine.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Animal Ethic committee approval has been collected and preserved by the author(s)

COMPETING INTERESTS

Author has declared that no competing interests exist.

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APPENDIX 1

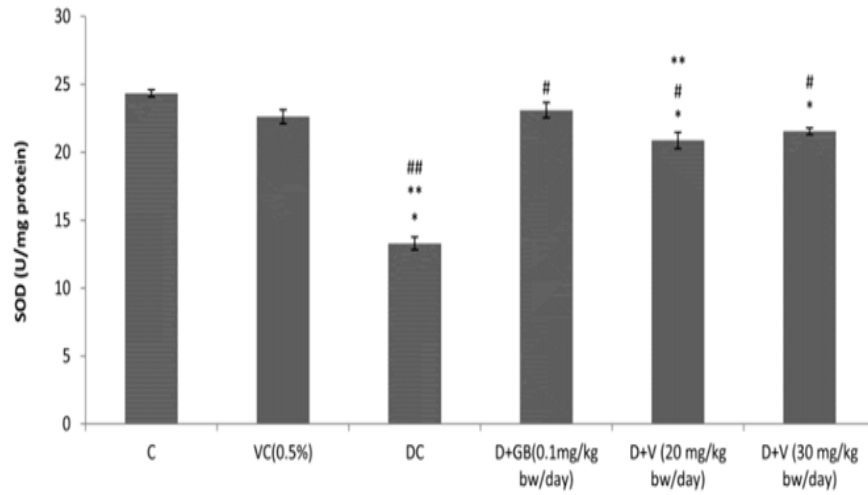


Fig. 3. Effect of vincamine on the activity of SOD of liver in diabetic rats

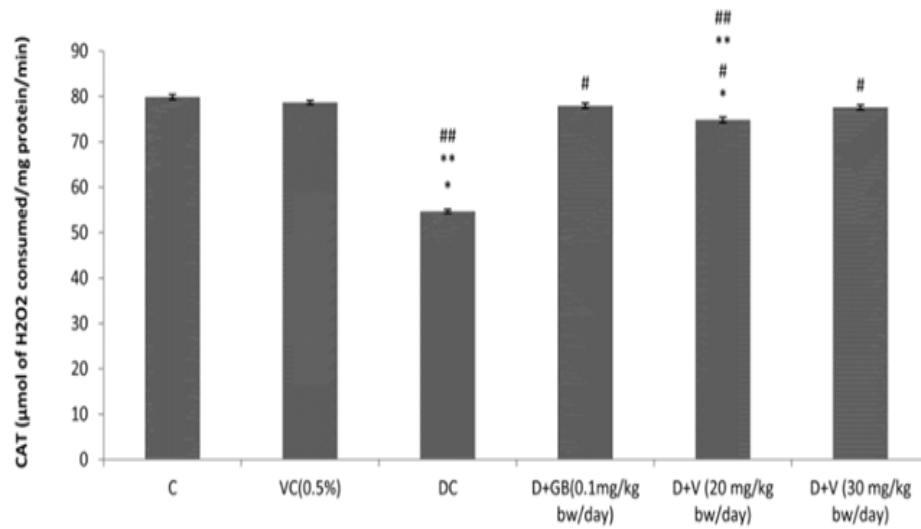


Fig. 4. Effect of vincamine on the activity of CAT of liver in diabetic rats

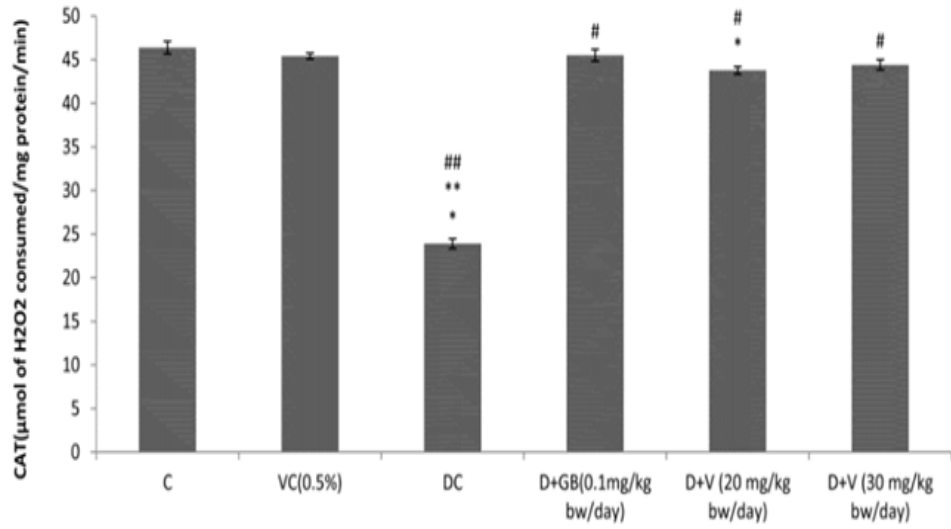


Fig. 5. Effect of vincamine on the activity of CAT of kidney in diabetic rats

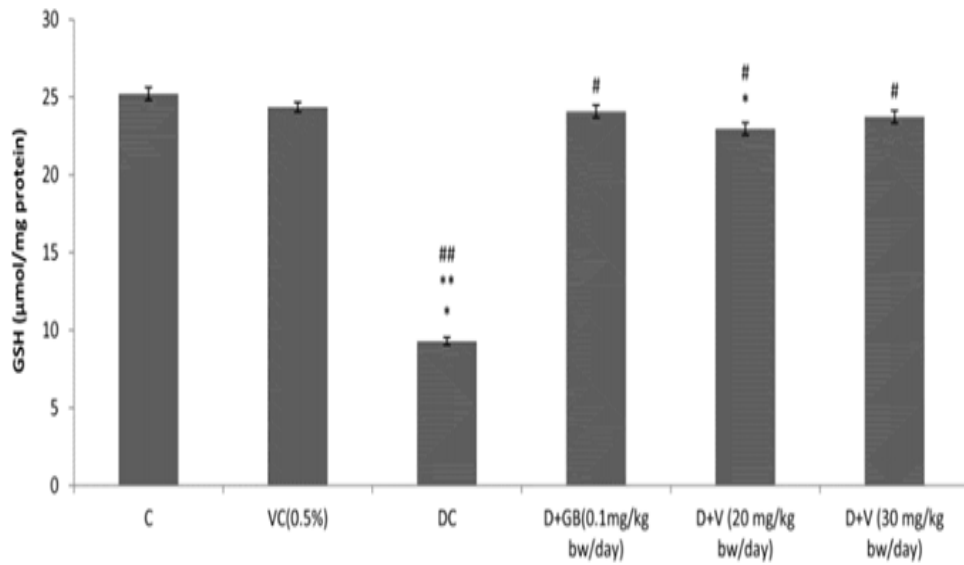


Fig. 6. Effect of vincamine on GSH level of liver in diabetic rats

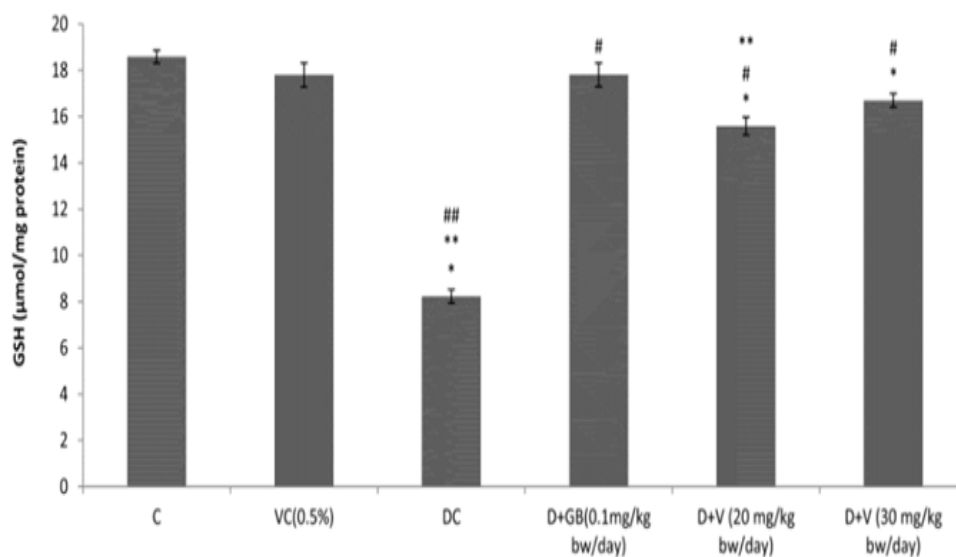


Fig. 7. Effect of vincamine on GSH level of kidney in diabetic rats

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