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AMELIORATED EFFECT OF COMBINED TREATMENT OF BLUEBERRY FRUIT EXTRACT AND VOGLIBOSE ON STREPTOZOTOCIN-INDUCED TYPE Ⅱ DIABETES MELLITUS IN RATS

Omnia E. Baheg[1,3,*], Mona E. Aboutabl[1], Nesrine S. El Sayed[2], Yousreya A. Maklad[1] and Sanaa A. Kenawy[2]

[1]*Medicinal and Pharmaceutical Chemistry Department, National Research Centre, 33–El Behouth St., 12622, Dokki, Giza, Egypt*
[2]*Pharmacology and Toxicology Department, Faculty of Pharmacy, Cairo University, Giza, Egypt*
[3]*Pharmaceutical and Drug Industries Research Division, National Research Centre, 33–El Behouth St., 12622, Giza, Egypt*

*Blueberries are rich in anthocyanins, which have been studied for many years. Interest in these compounds has grown attributing to their possible therapeutic and beneficial effects. Therefore, this study aimed to investigate the potential antioxidant, anti-inflammatory, hepatoprotective, anti-diabetic, and anti-inflammatory effects of blueberry fruit extract supplement (**25% anthocyanin**) in combination with aloglibtin and voglibose in streptozotocin (STZ)-induced diabetic rats.*

Diabetes mellitus was induced in six groups with a single 45 mg/kg STZ injection. However, 5 of these groups were treated with alogliptin (Alog), voglibose (Vog), blueberry fruit extract (BB-fruit extract), combined treatment of (Alog + BB-fruit extract), and (Vog + BB-fruit extract), respectively, for three weeks. Serum glucose, C-peptide, lipid profile, liver enzymes, kidney enzymes, and TNF-α levels were estimated. Meanwhile, alpha-glucosidase, catalase, and superoxide dismutase (SOD) activities and malondialdehyde (MDA) levels were determined in rats' liver tissues.

All diabetic groups unveiled a significant decrease in serum glucose and C-peptide level after administering BB-fruit extract. Combination of BB-fruit extract and vog is effective in achieving sufficient glycemic control by significantly reducing inflammation, oxidative stress, hyperlipidemia, and hyperglycemia. These findings imply that this combination is an effective strategy for controlling diabetes.

Keywords: *Type Ⅱ diabetes; Vaccinium uliginosum L.; Berries; Liver; Antioxidant*

INTRODUCTION

DM is a multiple-etiology metabolic disorder corresponding with high blood sugar levels resulting from deficient insulin secretion, action, or together due to deviations in carbohydrate, protein, and fat digestion. Furthermore, lipid metabolism problems, nephropathy, cardiomyopathy, and retinopathy are some of the consequences caused by persistent hyperglycemia[1]. Type 2 and type 1 are the two major classifications of diabetes. In insulin-dependent (IDDM) diabetes mellitus or type 1, the pancreatic β-cells are unable to manufacture insulin because of genetic factors or an autoimmune response. Whereas in type 2 diabetes mellitus, non-insulin-dependent (NIDDM), insulin is produced by the pancreas, but its receptors cannot execute their functions or are blocked because of a sedentary lifestyle

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*Corresponding author: Omnia E. Baheg, E-mail: omniabaheg@gmail.com

or other adaptive causes. IDDM accounts for 5-10% of all diabetes patients[2], whereas NIDDM is responsible for 90-95% of all instances of diabetes.

Furthermore, insulin output by the pancreas is adequate in type 2, but muscle tissue does not respond to insulin. However, this is mostly caused by infections, chemicals, drugs, pancreatic disease, surgery, environmental factors, or genetic defects in insulin action[2]. The World Health (WHO) Organization estimates that 439 million individuals worldwide will have diabetes in 2030[3&4]. Hyperglycemia induces oxidative stress, which significantly contributes to the pathophysiology of DM and its consequences[5-8].

The most popular medications used to treat DM include sulfonylureas, dipeptidyl peptidase-4 inhibitors, biguanides, α-glucosidase inhibitors, and thiazolidinediones; however, these therapies have limitations with higher adverse effects[9]. Prior research has demonstrated that α-glucosidase slows carbohydrate digestion rate and, consequently, the hyperglycemia level[10]. Synthetic medications have severe side effects, high costs, limited efficacy, and drug resistance. However, more than 150 plants are employed in treating DM based on the WHO. Alternative medicines derived from plants are currently prevalent and gaining increasing attention[11&12].

Food supplements or diets that contribute to controlling or preventing hyperglycemia may effectively reduce diabetes incidence[13]. Medicinal plants and many plant-based drugs provide a potential alternative therapy for DM due to their activities in maintaining glucose homeostasis and altering carbohydrate enzymes. In recent years, as a result of scientific research, berries have become increasingly important to humans, as they provide numerous health benefits and are rich in phytonutrients. However, their major flavonoids are flavonols, catechins, anthocyanin, and proanthocyanidins, while their hydroxylated phenolic acids are benzoic acid and cinnamic, which reduce hyperglycemia *via* α-amylase and α-glucosidase control[14]. Blueberry has significant medicinal potential against chronic disorders and is abundant in bioactive chemicals[15].

Moreover, the significance of medicinal plants stems from the fact that they are sources of potent and safer medications with relatively low side effects. Furthermore, exploring possible anti-diabetic drugs derived from plants requires pharmacological and chemical inquiry[16]. Thus, controlling blood HbA1c, glucose, hyperlipidemia, and hypertension is optimal for managing type 2 diabetes[17].

Thus, this research study intends to examine the impacts of the extract of blueberry on a diabetic animal model to understand the effects of blueberry extract on diabetes-related problems. In this work, diabetic Wistar rats were promoted *via* STZ, while diabetic and non-diabetic rats without supplementation served as controls. Meanwhile, *alogliptin* and *voglibose* were used as reference remedies.

MATERIALS AND METHODS

Experimental animals

The National Research Centre Giza, Egypt (animal colony) provided male albino Wistar rats (170 – 200 g). During the experiment period, animals were retained in groups of three in wire mesh plastic cages. Before commencing, animals were allowed seven days to adapt to the laboratory setting. Animals were housed under standardized circumstances: adequate ventilation, at 55 ± 5% relative humidity, a 12-hour dark/light cycle, and room (23 ± 2°C) temperature. The rats were provided with a typical pellet diet and given free availability to tap water. All studies were performed following the US National Institutes of Health's Handbook for the Care and Use of Laboratory Animals (NIH Publications No. 8023, revised 2011) and were authorized by the Ethics Committee for Animal Experiments at the Faculty of Pharmacy, Cairo University, Cairo, Egypt (Permit Number: PT 773). Furthermore, STZ (45 mg/kg) diluted in citrate buffer (0.1 mol/L, pH 4.5) was used to induce type 2 DM. Subsequently, administration of *alogliptin*, *voglibose*, blueberry fruit extract, and their combination began 48 hrs after diabetes inducement and lasted for 21 days.

Chemicals, supplements, and drugs

Sigma Aldrich (St. Louis, MO, USA) provided Streptozotocin ($C_8H_{15}N_3O_7$) (STZ). Anhui Ruisen Biological Technology Co., Ltd.

provided *alogliptin* as a gift. At the same time, *voglibose* was purchased from TCI fine chemicals Tokyo Chemical Industry Co., Ltd (TCI). Additionally, the fruit extract of the blueberry plant (*Genus Vaccinium*; Family *Ericaceae*; Species *Vaccinium uliginosum L.*) was purchased from Pharmswell Pharmaceutical, South Korea. The other substances were of high analytical quality. The analytical procedures utilized purified distilled water.

Diabetes induction

STZ injection (45 mg/kg, single intraperitoneally (i.p) dose) produced diabetes in rats deprived of food for 24 hours[18]. A glucose meter was employed to measure the glucose 72 hours after STZ injection (France, Bioneme). Rats with over 250 mg/dl blood glucose were deemed diabetic and utilized in this investigation[19]. Three days after STZ delivery, all treatments were initiated and sustained till the trial ended.

Experimental design

Two trials were conducted for this investigation. A pilot study was performed to choose the optimal dosage and duration of blueberry fruit extract treatment. Animals were assigned at random among five groups (n = 10); Group I (Normal) animals were administered a 7% diluted tween 80 solution (the vehicle for drugs preparation); Group II (Diabetic control): rats with diabetes without receiving therapy; Groups III (BB-extract 100), IV (BB-extract 200), and V (BB-extract 300) were orally treated for four weeks daily with 100, 200[20], and 300 mg/kg BB-extract, respectively. The 200 mg/kg dose of BB fruit extract was chosen to complete the current investigation because it considerably maintained normal body weights and lowered serum glucose levels compared to the other two doses.

In the main experiment, animals were randomly divided into seven groups (n = 10) and administered the medications every day for 21 days. Group I (Normal) rats were administered a 7% diluted tween 80 solution; Group II (Diabetic control): rats with diabetes without receiving therapy; Group III (*Alogliptin*) diabetic rats were orally administered *alogliptin* (10 mg/kg); Group IV (*Voglibose*) diabetic rats were orally administered *voglibose* (0.1 mg/kg); Group V (Blueberry extract) diabetic rats were orally administered the blueberry extract (200 mg/kg p.o.); Group VI (BB-extract + *Alogliptin*) diabetic rats were orally administered *alogliptin* and BB-extract; Group VII (BB-extract + *Voglibose*) diabetic rats orally administered *voglibose* and BB-extract. In the end, all rats were lightly anaesthetised by thiopental and euthanized by cervical dislocation and blood samples were collected under overnight fasting condition. Subsequently, for biochemical examination, serum was extracted, divided into aliquots, and stored at -80 degrees Celsius. Ultimately, the livers were dissected after scarification.

Liver Homogenate

The liver was excised immediately from all groups of animals and rinsed with ice-cold saline, perfused with cold phosphate-buffered saline (pH 7.4) to eliminate clots or blood cells.

Liver tissue (1 g) was homogenized for 3 minutes at 600 ×g in 50 mM potassium phosphate (10 ml, pH 7.4) cold buffer *via* a Potter-Elvehjem homogenizer with a Teflon pestle. Using a cooling centrifuge, the homogenate was spun for 20 minutes at 4°C and 3000 rpm (SIGMA 3K15, Germany). Lowry et al. (1951) 's method was utilized to determine the tissue homogenate's protein concentration. The supernatant was isolated and frozen at -80°C in aliquots for biochemical analysis.

Serum Biochemical Parameters.

Serum glucose levels were determined *via* a colorimetric assay kit (Biodiagnostics, Cairo, Egypt); while rat-specific ELISA kits from DRG Instruments, Marburg, Germany, were used to evaluate serum C-peptide levels. Serum high-density lipoprotein (HDL), triglycerides (TG), and total cholesterol (TC) levels were examined *via* Biodiagnostic kits (Cairo, Egypt) per the manufacturer's instructions. Kidney function was evaluated by serum creatinine and urea level examination. In addition, liver function was examined by glutamic-pyruvic transaminase (GPT), serum alkaline phosphatase (ALP), and glutamic-oxaloacetic transaminase (GOT) levels measurements *via* Biodiagnostic enzyme kits.

Determination of alpha-Glucosidase Activity.

Using Sigma-Aldrich, the alpha-glucosidase activity in liver homogenate was determined in accordance with Kim et al.'s method[21]. Briefly, alpha-glucosidase activity is evaluated *via* a process in which p-nitrophenyl-α-D-glucopyranoside was hydrolyzed by α-glucosidase, producing a colorimetric (405 nm) product proportionate to the amount of α-glucosidase activity.

Oxidative Stress Marker

Serum lipid peroxide was measured using the method published by Ohkawa et al.[22] to evaluate oxidative stress. However, MDA is a measure of lipid peroxidation that forms a pink complex in an acidic media with thiobarbituric acid. Therefore, this assay is TBARS, the thiobarbituric acid-reactive substance.

Antioxidant Enzymatic Activities

For the estimation of CAT and SOD activity, the methods described by Nishikimi et al.[23] and Aebi[24] were used, respectively.

Determination of Inflammatory Marker

The RayBio® Rat TNF-alpha ELISA (Enzyme-Linked Immunosorbent Assay) kit was used to quantify TNF-alpha[25,26].

Statistical analysis

All results were reported as mean ± S.E.M. The significance of the intergroup variation in the pilot study was determined using a two-way analysis of variance (ANOVA) and the Tukey test. Whereas one-way ANOVA followed by the Tukey test were conducted in the main study. GraphPad Prism version 6.05 was utilized to perform the statistical analysis. When $p \leq 0.05$, statistical significance was evaluated.

RESULTS AND DISCUSSION

Results

Effect of daily administration of different doses of BB-fruit extract on body weight and blood glucose levels

The diabetes group had considerably higher glucose levels in their blood than the control group ($p < 0.05$). All doses (100, 200, 300 mg/kg) of blueberry fruit extract (25% anthocyanins) administered orally effectively lowered blood glucose levels (Table 1).

Table 1: Effect of oral daily administration of the different doses of BB-fruit extract on changes in body weight and blood glucose levels.

Groups	Blood Glucose (mg/dl) Time (days)						Body Weight Time (days)	
	Zero	48 hrs	7 Days	14 Days	21 Days	28 days	Zero	28 days
Normal	93.67 ±2.03	95.17^{b} ±2.71	96.00^{b} ±2.17	94.50^{b} ±2.79	92.33^{b} ±2.60	94.17^{b} ±2.08	174.5 ±3.44	217.7^{b} ±6.97
Diabetic control	95.53 ±1.20	529.62^{a} ±12.67	473.22^{a} ±10.91	489.45^{a} ±11.77	443.62^{a} ±10.67	526.40^{a} ±14.67	173.2 ±3.13	134.7^{ac} ±2.94
BB-extract 100	95.83 ±2.10	381.24^{ab} 11.51	410.20^{ac} ±18.86	373.26^{abc} ±10.33	347.22^{abc} ±18.28	311.21^{abc} ±17.29	144 ±5.58	143.2^{ac} ±6.56
BB-extract 200	95.62 ±0.95	323.62^{ab} ±9.79	237.42^{ab} ±8.09	148.32^{b} ±7.71	102.50^{b} ±7.36	99.42^{b} ±7.11	178 ±7.32	206.7^{b} ±9.52
BB-extract 300	94.28 ±1.02	397.21^{ab} ±11.36	330.15^{ab} ±7.77	279.5^{0abc} ±13.56	240.31^{abc} ±12.75	226.20^{abc} ±13.55	169 ±8.27	182.8^{b} ±6.96

STZ-induced diabetic rats oral daily administered different doses of BB-fruit extract (100, 200, 300 mg/kg) for 28 days. Values expressed as mean ± S.E.M; (n = 10; $p < 0.05$; a vs normal; b vs diabetic control; c vs BB-extract 200), two-way ANOVA followed by Tukey's post hoc test.

Effect of alogliptin, Voglibose, BB-fruit extract supplement and their combination on glucose metabolism

Rats with diabetes displayed hyperglycemia, as evidenced by a 433.05 percent rise in glucose levels compared to the normal group. Compared to the diabetic group, daily therapy with *Alog*, *Vog*, or BB-fruit extract significantly decreased glucose levels by 53.85, 70.41, and 58.22%, respectively. The combination of *Alog* and BB-fruit extract did not affect the serum glucose level compared to the respective results of the individual treatments. Whereas co-administration of both *Vog* and BB-fruit extract acted synergistically to normalize the serum glucose level **(Fig. 1A)**. In addition, the serum C-peptide level of STZ-treated mice was significantly reduced by 61.79% compared to the normal group. Treatment with *Alog*, *Vog*, or BB-fruit extract did not significantly alter the serum C-peptide level relative to the diabetic value. Furthermore, co-administration of BB-fruit extract and *Alog* had no significant effect on the serum C-peptide levels of diabetic rats. The combination of *Vog* and BB-fruit extract ameliorated the reduction in serum C-peptide induced by STZ in diabetic rats by restoring serum C-peptide to its normal value (Fig. 1B).

Effect of Alogliptin, Voglibose, BB-extract and their combination on alpha-glucosidase concentration

STZ-induced diabetes in rats showed a significant reduction in alpha-glucosidase concentration in liver homogenate by 35.07%, in comparison to the corresponding normal value. Individual treatment of *Alog* in diabetic rats did not significantly alter alpha-glucosidase concentration. In contrast, treatment of diabetic rats with *Vog*, BB-fruit extract, or a combination of *Alog* and BB-fruit extract significantly increased alpha-glucosidase activity in liver homogenate by 52.40%, 55.08%, and 28.34%, respectively, compared to the corresponding diabetic values. Moreover, combined treatment with *Vog* and BB-fruit extract induced a significant increase in alpha-glucosidase content in liver homogenate by 88.77% compared to the corresponding diabetic values **(Fig. 1C)**.

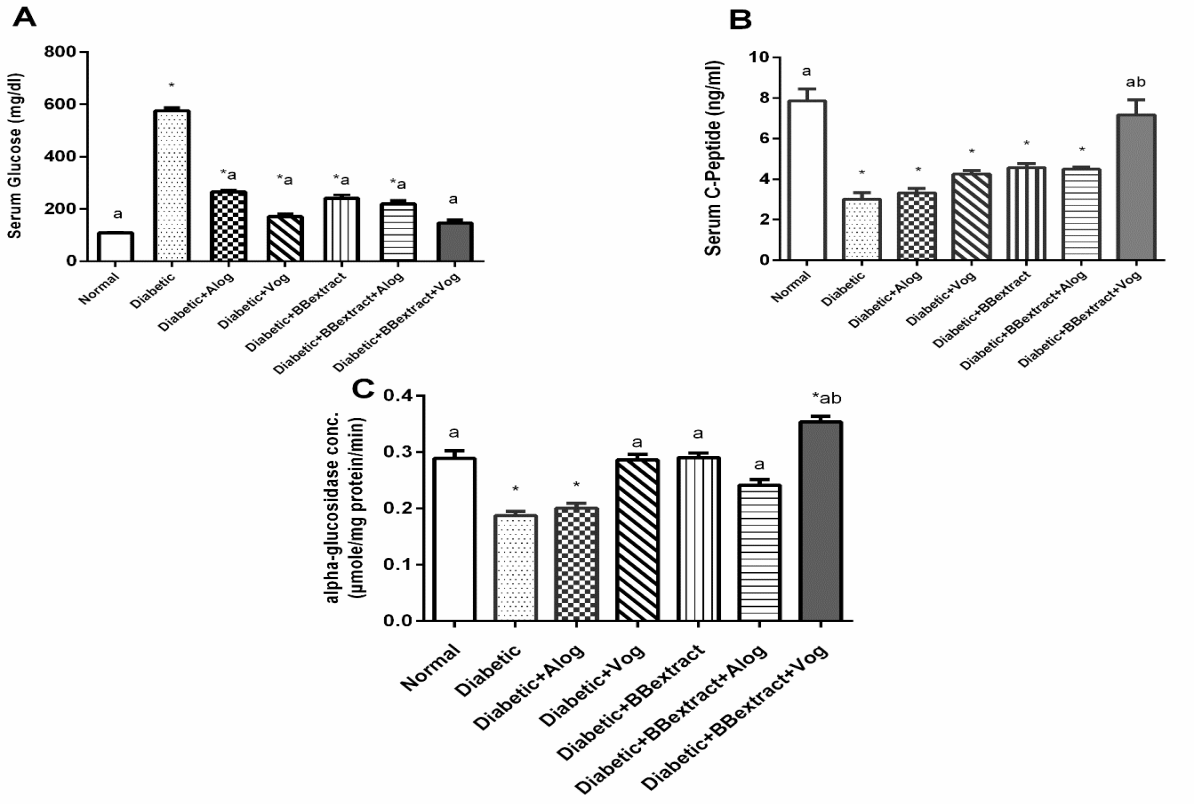

Fig. 1: Effect of daily administration of *alogliptin*, *Voglibose*, BB-fruit extract, and their combination on glucose metabolism in diabetic rats. *Voglibose* (0.1 mg/kg), *alogliptin* (10 mg/kg), BB-fruit extract (200 mg/kg), and their combination were administered orally to diabetic rats once a day for three weeks.

Effect of alogliptin, Voglibose, BB-extract and their combination on serum TC, TG, and HDL

With the induction of diabetes, blood TC, TG, and low-density lipoprotein (LDL) levels increased by 113.61%, 119.84%, and 467.43%, respectively, compared to their respective normal values, whereas serum HDL levels decreased by 34.55%. In comparison to the diabetic control value, neither *Alog* nor *Vog* resulted in a significant change in blood TC and TG levels. BB-extract significantly decreased serum TC, TG, and LDL by 17.28%, 16.23%, and 28.27%, respectively, compared to the corresponding diabetic values. Co-administration of blueberry fruit extract with *voglibose* synergistically decreased serum TC and TG levels and restored the serum HDL to its normal value **(Fig. 2)**.

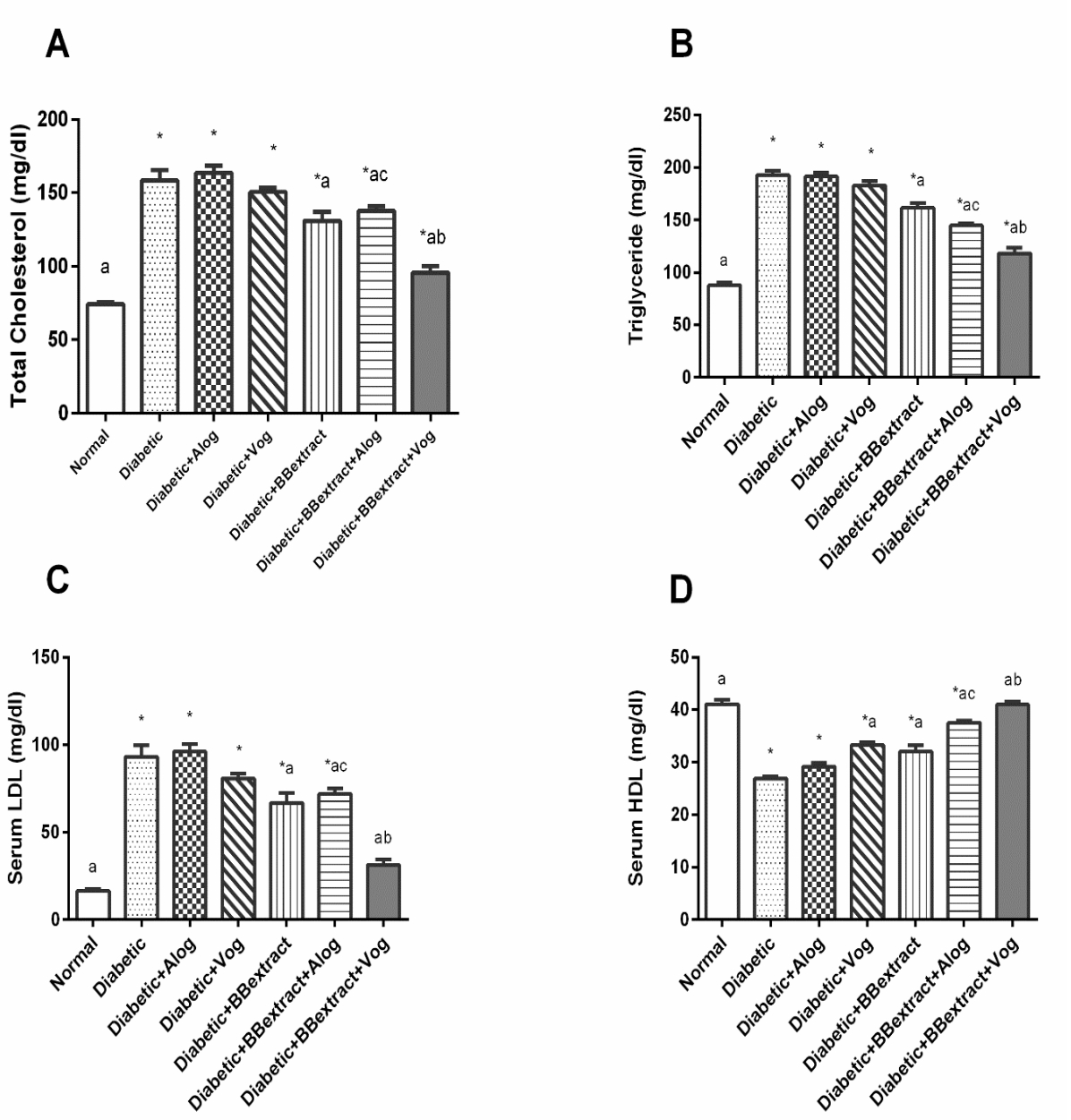

Fig. 2: Effect of daily administration of *Alog*, *Vog*, BB-fruit extract and their combination on the rat's serum TC, HDL, LDL, and triglyceride in diabetic rats.

Effect of alogliptin, Voglibose, BB-extract and their combination on liver and kidney functions

Serum creatinine and urea increased significantly in diabetic rats by 102.40% and 130%, respectively, compared to the normal value. Treatment with BB-fruit extract individually or in combination with Vog induced a significant decrease in serum creatinine level by 17.85% and 29.76%, respectively, compared to the diabetic value. In addition, co-administration of *Vog* and BB-fruit extract acted synergistically to restore the serum urea to its normal level. On the other hand, administration of *Alog*, Vog, or combined treatment with *Alog* and BB-fruit extract didn't induce any significant changes in serum creatinine level compared to that of diabetic value (Table 2).

The serum GOT, GPT, and ALP levels of diabetic rats are significantly elevated by 37.78, 47.26, and 56.35%, respectively, compared to the respective normal value. Combined treatment with *Vog* and BB-fruit extract for three weeks restored the serum GOT, GPT, and ALP to their normal level (Table 2).

Effect of alogliptin, voglibose, BB-fruit extract supplement and their combination on inflammatory biomarkers and oxidative stress

STZ-induced diabetes in rats resulted in a 47.30% decrease in the SOD concentration of liver homogenate relative to its normal value. Oral daily administration of *Alog* didn't induce any significant change in SOD concentration compared to diabetic value. The SOD concentration of diabetic rats treated with either *Vog* or BB-fruit extract increased by 51.60 and 38.48 percent, respectively, compared to diabetic values. Moreover, three weeks of combined treatment with *Alog* and BB-fruit extract significantly increased the SOD concentration by 33.30% compared to the corresponding diabetic value. Conversely, co-administration of *Vog* and BB-fruit extract normalized the SOD level by a synergistic effect **(Fig. 3A).**

In comparison to the normal value, the concentration of catalase in diabetic rats was significantly reduced by 65.53%. Treatment with *Alog*, *Vog*, or BB-fruit extract resulted in significant increases in catalase concentration of 61.01%, 97.79%, and 106.58%, respectively, compared to the diabetic value. In diabetic rats, co-administration of *Alog* or *Vog* with BB-fruit extract increased catalase concentration by 35.13 and 22.50%, respectively, compared to treatment with *Alog* or *Vog* alone **(Fig. 3B)**.

STZ significantly increased MDA concentration by 115.47% of its normal value to be 6.96 ± 0.35 µmol/mg protein. However, the MDA level was not significantly altered by *Alog*. On the other hand, combined treatment with *Alog* and BB-fruit extract induced a significant decrease in MDA concentration by 23.70% and 20.63% compared to the corresponding diabetic and *alogliptin*-treated values, respectively. The MDA content of diabetic rats treated with either *Vog* or BB-fruit extract decreased significantly by 19.39% and 17.50%, respectively, compared to the diabetic value. Additionally, co-administration of *Vog* and BB-fruit extract decreased the MDA levels by 20.15% relative to diabetic rats treated with *Vog* alone **(Fig. 3C)**.

The serum TNF-alpha level of diabetic rats was significantly elevated by 139.46% compared to the normal value. *Alog* significantly reduced serum TNF-alpha by 26.39% compared to the diabetes value. Meanwhile, Vog, BB-fruit extract, and concurrent administration of *Alog* or Vog with BB-fruit extract acted synergistically to normalize the serum TNF-alpha level **(Fig. 3D)**.

Serum levels of (A) glucose, (B) C-peptide, and (D) alpha-glucosidase concentration. (mean ± S.E.M; n = 10 animals; *vs. normal; a vs. diabetic control; b vs. *voglibose* + BB-fruit extract (One-way ANOVA followed by Tukey's post hoc test; $p < 0.05$).

Three weeks of daily oral administration of *alogliptin* (10 mg/kg), *voglibose* (0.1 mg/kg), BB-extract (200 mg/kg), or their combination were administered to diabetic rats. Serum (A) TC, (B) TG, (C) LDL, (D) HDL. (mean ± S.E.M; n = 10 animals; * vs. normal; a vs. diabetic control; b vs. *Vog* + BB-extract; c vs. *Alog* + BB-fruit extract (One-way ANOVA followed by Tukey's post hoc test; $p < 0.05$).

Levels of (A) SOD, (B) Catalase, (C) MDA in liver homogenate, and serum (D)TNF-α. (mean ± S.E.M; n = 10 animals; * vs. normal; a vs. diabetic control; b vs. *Vog* + BB-extract; c vs. *Alog* + BB-extract (One-way ANOVA followed by Tukey's post hoc test; $p < 0.05$).

Table 2: Effects of *Alog*, *Vog*, and BB-fruit extract on the rat's serum creatinine, urea, GPT, GOT, and ALP .

	Non-Diabetic Rats (n = 8)	**Diabetic rats**					
		Diabetic control	**Alog (10 mg/kg)**	***Vog* (0.1 mg/kg)**	**BB-extract**	***Alog* (200 mg/kg)**	***Vog* +BB-extract**
Creatinine (mg/dl)	0.83^{a} ± 0.01	1.68^{*} ± 0.08	1.76^{*} ± 0.02	1.65^{*} ± 0.02	1.38^{*a} ± 0.05	1.70^{*} ± 0.03	1.18^{*ab} ± 0.03
Urea (mg/dl)	40.34^{a} ± 1.57	92.82^{*} ± 2.93	83.22^{*} ± 2.63	77.91^{*a} ± 1.08	65.73^{*a} ± 4.38	84.10^{*} ±3.30	55.66^{ab} ± 2.10
SGPT (U/L)	79.65^{a} ± 2.87	117.30^{*} ± 8.37	95.63^{*a} ± 3.42	101.70^{*} ± 7.84	75.23^{a} ± 6.62	95.86^{*a} ± 1.88	70.12^{ab} ± 2.69
SGOT (U/L)	105.60^{a} ± 2.87	145.50* ± 8.37	124.30*a ± 4.79	139.60* ± 3.31	104.80^{a} ± 6.62	118.20^{a} ± 4.04	97.86^{ab} ± 4.03
ALP (U/L)	110.90^{a} ± 1.29	173.40^{*} ± 2.45	138.00^{*a} ± 0.96	28.00^{*a} ± 1.96	127.80^{*a} ± 3.40	124.00^{*ac} ± 1.98	105.00^{ab} ± 1.07

SGPT, serum glutamic-pyruvic transaminase; SGOT, serum glutamic-oxaloacetic transaminase; ALP, alkaline phosphatase. (mean ± S.E.M; n = 10; $p < 0.05$; * vs. normal; a vs. diabetic control; b vs. *voglibose* + BB-fruit extract; c vs. *alogliptin* + BB-fruit extract), one-way ANOVA, Tukey-Kramer post hoc test.

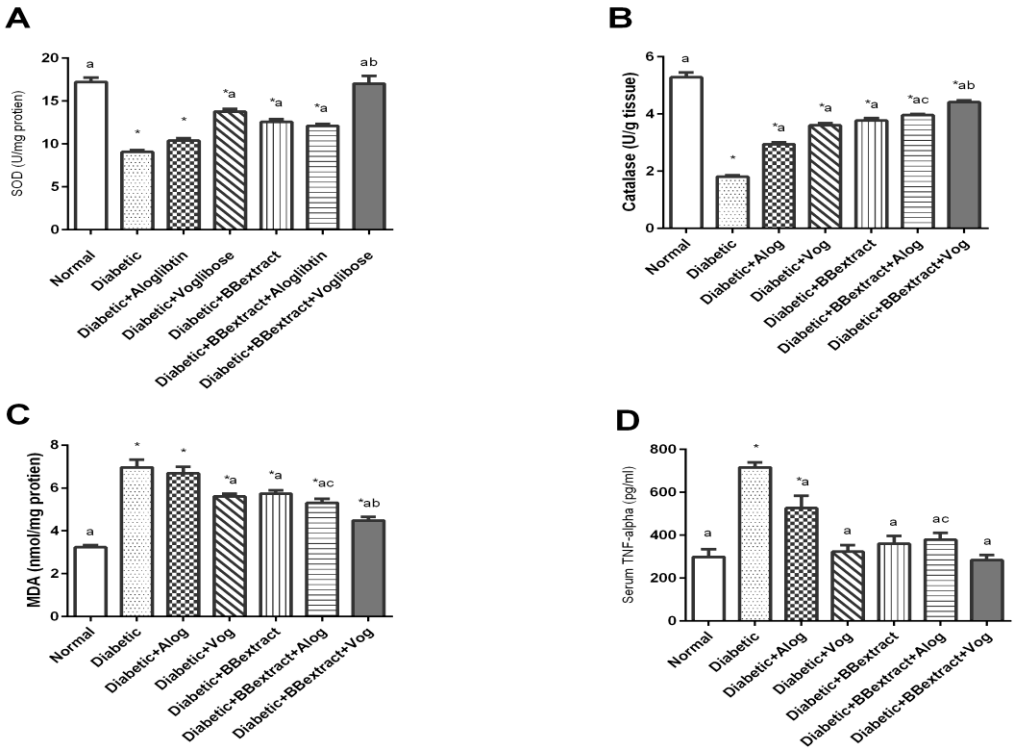

Fig. 3: Effect of daily administration of *Alog*, *Vog*, BB-fruit extract and their combination on the oxidative and inflammatory status in diabetic rats. *Alog* (10 mg/kg), *Vog* (0.1 mg/kg), BB-fruit extract (200 mg/kg), and their combination were administered orally to diabetic rats once a day for three weeks.

Discussion

DM is the illness with the highest prevalence of mortality and morbidity and the fastest growth rate globally. This chronic illness cannot be cured, but it can be controlled. However, natural products and traditional plant treatments have been used for ages to alleviate the symptoms of diabetes. The present investigation provides persuasive evidence in support of the combination of *Voglibose* (*Vog*) and BB-fruit extract (200 mg/kg) for treating rats with diabetes. The concomitant administration of *Vog* and BB-fruit extract significantly enhanced the antioxidant, anti-hyperlipidemic, anti-inflammatory, and anti-diabetic benefits compared to either medication alone.

In the ongoing investigation, STZ resulted in a marked drop in C-peptide level and a considerable increase in glucose level; these effects were only reversed by the concurrent administration of BB-fruit extract (200 mg/kg) and *Vog* (0.1 mg/kg). Individual administration of *Alog*, Vog, and BB-fruit extract decreased glucose levels without a corresponding change in C-peptide concentration compared to the diabetic group. Consistent with Zhang et al.[27], prolonged treatment of diabetic rabbits with *Alog* (25 mg/kg) decreased glucose concentration without a change in serum insulin level relative to diabetic rabbits. In addition, Moritoh et al.[28] found that *Alog* only induced glycaemic control and marginally improved basal plasma insulin levels; thus, the DPP-4 inhibitors *vildagliptin* and *sitagliptin* unable to enhance these parameters in experiments with db/db mice that were similarly structured. In addition, *Alog* alone had no noticeable impact on pancreatic insulin levels in db/db animals or PDX1 expression and insulin in the islets[29]. These inhibitors lengthen total carbohydrate digestion time and delay carbohydrate digestion, resulting in a slower glucose absorption rate and lower postprandial plasma glucose rise[30]. Carbohydrate absorption from the small intestine is inhibited by alpha-glucosidase inhibitors, which inhibit enzymes that transform complicated non-absorbable carbs into simple absorbable carbohydrates through competitive inhibition. Included among these enzymes are isomaltase, maltase, glucoamylase, and sucrase. They minimize the rise in postprandial blood glucose by approximately 3 mmol/l by delaying carbohydrate absorption[30]. Demir et al.[31] and Umamageswari et al.[32] explored the hypoglycemic effect of the aqueous and alcoholic extracts of berries in diabetic Wistar rats provoked by alloxan and STZ. Thus, flavonoids could be the active component responsible for the activity in the extracts[33].

α-Glucosidase concentration in diabetic rats' liver was significantly inhibited, which is consistent with Otsuki and Williams and Aly et al.'s findings[34&35] showed the reduction in digestive enzymes amount released from diabetic rats acini, leading to reduced alterations in nutritional, secretary capacity, or other hormones states, and a decrease of secretagogues or a combination of these factors. *Alog* didn't induce a significant change in α-glucosidase concentration in liver homogenate relative to diabetes. Diabetic rats' treatment with BB-fruit extract significantly increased the alpha-glucosidase level in liver homogenate. Therefore, berries can lower hyperglycemia by regulating the α-amylase and α-glucosidase enzymes[14].

In this work, diabetic rats exhibited a rise in TC, LDL, and TG, as well as a drop in HDL. This changed lipid profile induces cardiovascular disease[36]. Several investigations have found modified serum lipids in insulin-resistant rats, in agreement with our findings[37-39]. The atherogenic lipid profile can cause liver lipid buildup and consequent hepatocyte injury[40]. In the current investigation, daily therapy with *alogliptin* or *voglibose* did not influence TG, LDL, or TC levels in the diabetic group; however, *voglibose* dramatically increased HDL levels.

In contrast, daily therapy with BB-fruit extract decreased the LDL, TG, and TC levels, whereas it increased the HDL level. However, berries were found to alleviate hyperlipidemia, considerably enhance blood HDL, and reduce the concentrations of LDL, TG, and TC in diabetic rats[41]. In addition, the combination treatment operated synergistically, resulting in a considerable drop in blood LDL, TG, and TC levels compared to the *Vog*-treated diabetic rats and a return to normal serum HDL levels.

Further, liver enzyme levels, including SGOT, SGPT, ALP, and AST, as well as kidney function (creatinine), were significantly

elevated in diabetic rats. However, catechin (Flavonoid in berries) may have a protective impact against STZ function through regulating oxidative stress[41&42].

Notable relationships exist between oxidative stress, hyperglycemia, and inflammation[43&44]. Hyperglycemia-induced oxidative stress can promote insulin resistance and disrupt insulin signaling. In this study, STZ decreased CAT and SOD antioxidant levels and increased hepatic lipid peroxidation. In diabetes, reactive oxygen species can trigger the peroxidation of the cell membrane polyunsaturated fatty acids, leading to cell damage that induces diabetic complications, such as retinopathy and nephropathy. Hyperglycemia can also decrease antioxidants within cells.

Moreover, Mahmoud et al.[8] found that the HFD/STZ decreased the antioxidants level and increased the MDA level, which is consistent with our findings. Additionally, treatment with *Voglibose*, BB-fruit extract, and combined treatment with *alogliptin* and BB-fruit extract in diabetic rats decreased MDA levels, as well as increased CAT and SOD levels. Combined treatment with *Vog* and BB-fruit extract restored SOD and MDA in liver homogenate to their normal levels.

Satoh et al.[45] explored that *Vog* decreased soluble intercellular adhesion molecule 1 and oxidative stress production in type 2 DM concurrently with reducing postprandial hyperglycemia and hyperlipidemia. With the administration of the blueberry extract, Albrahim and Alonazi [46] found a substantial reduction in oxidative stress in aged rats. In a rat model, berry extracts and blueberries exhibit antioxidant and anti-inflammatory properties[47]. However, the blueberry extract has greater antioxidant activity than individual ones[48&49]. Many types of research demonstrate a linear relationship between total phenolic contents, anthocyanins in blueberries, and antioxidant activity[50&51].

Hyperglycemia also stimulates inflammatory cytokines production, which may be mediated by excessive ROS creation and an immunostimulatory response [52,53]. According to previous research, inflammation is believed to be the root cause of numerous problems in DM, such as atherosclerosis[54-56]. According to the findings of the present investigation, hyperglycemia increased serum TNF-alpha levels relative to normal. In this work, *Alog* decreased the TNF-alpha of the diabetic group. In diabetic rats, *Vog*, BB-fruit extract, and their combination for three weeks restored serum TNF-alpha to normal levels. In addition, treatment with *Alog* and BB-fruit extract (200 mg/kg/day, p.o.) normalized the serum TNF-alpha level in a synergistic manner. Studies on animals have demonstrated that the DPP-4 inhibition effect on inflammation and atherosclerosis is mediated by chemotaxis and monocyte inhibition[57&58]. *Alogliptin* reduced the TLR-4-mediated production of IL-6, IL-1, and other pro-inflammatory cytokines by mononuclear cells, according to previous research[59]. In addition, Purnachander et al.[60] found that diabetic rat treatment with *alogliptin* for four weeks had a substantial decrease in TNF-α.

Similarly, alpha-glucosidase inhibitors decreased glucose through their anti-inflammatory effects. Further, miglitol, through reducing glucose fluctuations in hyperglycemia, decreases the gene expression of inflammatory cytokines/cytokine-like factors in peripheral leukocytes. In addition, Derosa et al.[61] discovered that acarbose was more successful in lowering the pastoral fat-load peaks of different parameters, such as inflammatory markers and insulin resistance.

Similarly, Albrahim and Alonazi[46] demonstrated that injection of blueberry extract dramatically reduced TNF-α levels in the livers of elderly rats, suggesting its significance in inhibiting molecular inflammatory pathways. *In vivo* and *in vitro* research on metabolic impairment has highlighted the anti-inflammatory and antioxidant properties of blueberries. In obese Zucker rats treated with blueberry extract powder, a positive inflammatory response was seen[62]. Ingestion of a meal rich in wild blueberries substantially decreased IL-6, TNF-α, and C reactive protein levels (CRP). In addition, CRP expression decreased in the liver, whereas NF-*κ*B, IL-6, and TNF-α were downregulated in both the abdominal adipose and liver tissues[62].

Conclusion

This study concludes that the combination of blueberry fruit extract and v*oglibose* is effective in achieving sufficient glycemic

control by significantly reducing inflammation, oxidative stress, hyperlipidemia, and hyperglycemia. These findings imply that this combination is an effective strategy for controlling diabetes.

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نشرة العلوم الصيدليـــة
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التأثير المحسن للعلاج المتزامن لمستخلص فاكهة التوت والفوجليبوز في الجرذان المستحدث فيها داء السكري بالستربتوزوتوسين

أمنية بهيج[١،٣*] – منى أبو طبل[١] – نسرين السيد[٢] – يسرية مقلد[١] – سناء أ. قناوي[٢]

[١] قسم الكيمياء الطبية والصيدلانية، المركز القومي للبحوث، ٣٣ شارع البحوث، ١٢٦٢٢، الدقي، الجيزة، مصر

[٢] قسم علم الأدوية والسموم ، كلية الصيدلة ، جامعة القاهرة ، الجيزة ، مصر

[٣] شعبه بحوث الصناعات الدوائية والدوائية ، المركز القومي للبحوث ، ٣٣ شارع الحوث ، ١٢٦٢٢ ، الجيزة ، مصر

يزداد انتشار وحدوث داء السكري من النوع ٢ عالمياً بصورة متزايده. ومن المتوقع ان يصبح داء السكري السبب السابع المؤدي للوفاة بحلول عام ٢٠٣٠ وفقا لأحدث التقديرات الصادرة عن منظمة الصحة العالمية . التوت غني بالأنثوسيانين، يوجد اهتمام بهذه المركبات بسبب آثارها العلاجية والمفيدة المحتملة. لذلك ، يهدف البحث الحالي الي دراسة الآثار المستفادة المحتملة من لمضادات الأكسدة ، ومضادات الالتهابات ، ووقاية الكبد ، ومضادة لمرض السكري ، ومضادة للالتهابات من مكمل مستخلص فاكهة التوت الأزرق (٢٥٪ أنثوسيانين) (٢٠٠مجم/كجم) و العلاج المتزامن له مع الألوجلبتين (١٠مجم/كجم) أوالفوغليبوز(٠,١ مجك/مجم) عن طريق الفم على التوالي لمدة ثلاثة أسابيع كعلاج لمرض السكري المستحدث باستخدام مادة الاستربتوزوتوسين (٤٥ مجم/كجم) في التجويف البريتوني في الجرذان. وتم قياس مستوي كل من الجلوكوز، بيبتيد سي، الكوليستيرول الكلي، الدهون الثلاثية، إنزيمات الكبد، إنزيمات الكلى، معامل التنكرز الورمي ألفا، في المصل. وفي الوقت نفسه ، تم تحديد محتوى ألفا جلوكوزيداز، الكاتلاز، ديسموتاز الفائق، ومستويات بيروكسيد الدهون في أنسجة كبد الفئران.

أحدث استخدام مستخلص فاكهة التوت البري متزامنا مع فوغليبوز في تحقيق السيطرة الكافية على نسبة السكر في الدم عن طريق الحد بشكل كبير من الالتهاب ، والإجهاد التأكسدي ، و زيادة الكوليستيرول الكلي و الدهون الثلاثية. حدث تحسن ملحوظ في مستوي الجلوكوز وبيبتيد سي عند تناول تـوتلا ةهكاف صلختسم متزامنا مع زوبيلغوف وهذا التحسن كان أفضل من التأثير المنفرد لكل منهما.