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Cardiac Oxidative Status in Diabetic Wistar Rats Exposed To Ethanol Extract of *Cucumis Sativus* Fruit

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ABSTRACT

The present study investigated cardiac oxidative status in diabetic Wistar rats exposed to ethanol extract of *Cucumis sativus* fruit. Male Wistar albino rats (n = 25, mean weight = 215 ± 15 g) were randomly assigned to five groups of 5 rats each: normal control, diabetic control, metformin, extract (200 mg/kg body weight, bwt) and extract (300 mg/kg bwt) groups. Diabetes mellitus was induced in the rats via intraperitoneal injection of 50 mg/kg bwt STZ. The diabetic rats were treated for 21 days with either metformin (50 mg/kg bwt) or the extract. Activities of antioxidant enzymes such as catalase, superoxide dismutase (SOD), glutathione peroxidase (GPx) and glutathione reductase (GR) as well as molecules like reduced glutathione (GSH), total protein (TP), malondialdehyde (MDA) and nitric oxide (NO) were measured in heart homogenate. The results showed that induction of diabetes mellitus with STZ significantly increased the fasting blood glucose (FBG) concentrations of the rats, while decreasing the activity/concentration of antioxidant enzymes/molecules ($p < 0.05$). However, treatment of the diabetic Wistar rats with the extract markedly reduced the FBG concentration and body weights of rats, but enhanced the activity/concentration of antioxidant enzymes/molecules in cardiac tissue ($p < 0.05$). These results indicate that ethanol extract of the medicinal plant fruit has the potential to promote antioxidant defense in the heart of STZ-induced diabetic rats.

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Introduction

The heart is a muscular organ which pumps blood through the blood vessels of the circulatory system [1]. Blood provides the animal's body with oxygen and nutrients as well as assist in the removal of metabolic wastes. In humans, the heart is located between the lungs in the middle compartment of the chest [2-4]. The heart is effectively a syncytium, a meshwork of cardiac muscle cells interconnected by contiguous cytoplasmic bridges [5-7]. Cardiac injury induced by drugs is becoming an increasingly important concern, since it constitutes serious risk to human health [8]. Cardiac dysfunction caused by cardiotoxic agents such as STZ may lead to heart failure, myocardial ischemia, arrhythmias, hypertension, myocarditis, pericarditis, and thromboembolism [9]. Oxidative and nitrate stress, as well as protein adduct formation are established mechanisms of chemical-induced cardiotoxicity. The latter leads to cardiomyocyte inflammation, altered calcium homeostasis, programmed cell death (apoptosis), swelling of cardiomyocytes, nuclear splitting, vacuolization, and alteration in signaling pathways. These events result in diseases of the heart muscle including heart failure, which could lead to death [10].

Diabetes mellitus is generally induced in laboratory animals by several methods: chemical, surgical and genetic (immunological) manipulations. Chemical method include the use of STZ, alloxan

and sucrose load. Synthesized by a strain of the soil microbe *Streptomyces achromogenes* (gram positive bacterium) STZ is a permanent diabetes inducing drug [11]. Discovered in 1959 as an antibiotic STZ is an unusual aminoglycoside containing a nitrosoamino group. The nitrosoamino group enables the metabolite to act as a NO donor. Streptozotocin is widely used to induce diabetes mellitus in rodent models via inhibition of β -cell O-GlcNAcase [12]. It is widely used to induce both insulin-dependent (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM) [13,14]. It is both an antibiotic and an antitumor agent, and induces diabetes mellitus via reduction of nicotinamide adenine dinucleotide in pancreatic β -cells *in vivo* [14]. This study investigated cardiac oxidative status in diabetic Wistar rats exposed to ethanol extract of *C. sativus* Fruit.

Materials and Methods
Chemicals

All chemicals and reagents used in this study were of analytical grade and they were products of Sigma-Aldrich Ltd. (USA).

Plant Extraction

Freshly harvested *Cucumis sativus* fruits were purchased from a major fruit/vegetable market in Benin City, Nigeria and identified by Dr. Henry Akinnibosun of Plant Biology and Biotechnology Department, University of Benin. They were thereafter washed, and air-dried for about 4 weeks at the Department of Biochemistry. The dry plant was ground with a mechanical blender. The pulverized

sample was cold macerated in absolute ethanol for three days (72 h) in a bell jar and filtered using Whatmann filter paper No. 42 (125 mm). The ethanol extract was thereafter concentrated using rotary evaporator and freeze-dried using a lyophilizer [15-17].

Experimental Animals

Mature male Wistar albino rats (n = 25, mean weight = 215 ± 15 g) were bought from the Department of Anatomy, University of Benin, Nigeria and housed in wooden cages. They were acclimatized for two weeks before commencement of the study, and had free access to feed and water.

Experimental Design

The rats were randomly assigned to five groups (5 rats/group): normal control, diabetic control, metformin, extract (200 mg/kg bwt) and extract (300 mg/kg bwt) groups. Diabetes mellitus was induced in the rats via intraperitoneal injection of 50 mg/kg bwt STZ. The diabetic rats were then treated with either the standard antidiabetic drug metformin (50 mg/kg bwt) or the extract at doses of 200 and 300 mg/kg bwt, respectively, for 21 days.

Tissue Sample Collection and Preparation

At the end of day 21 of treatment, the rats were euthanized under mild chloroform anaesthesia after an overnight fast. Their hearts were excised, and used to prepare 20 % tissue homogenate. The

homogenate was centrifuged at 2000 rpm for 10 min to obtain supernatant which was used for biochemical analysis.

Biochemical Analyses

The activities of catalase, SOD and GPx were determined [18-20]. Cardiac levels of TP, MDA, GSH, and NO were also measured [21-28]. The activity of GR was determined using a previously described method [29].

Statistical Analysis

Data are presented as mean ± SEM (n = 5). Statistical analysis was performed using SPSS version 21. Statistical differences between means were compared using Duncan multiple range test. Statistical significance was assumed at p < 0.05.

Results

Effect of ethanol extract of *C. Sativus* on weight and blood glucose of rats

As shown in Tables 1 and 2, induction of diabetes mellitus using STZ significantly increased the blood glucose concentration of the rats (p < 0.05). However, treatment of the diabetic rats with extract of *C. sativus* fruit markedly reduced their FBG concentration and body weights, but increased the weight of their hearts as well as the relative organ weight (p < 0.05).

Table 1: Effect of ethanol extract of *C. Sativus* on weight and blood glucose parameters

Group	Weight Change (g)	% Weight Change	FBG (mg/dL)	Glycemic Change (mg/dL)	% Glycemic Change
Normal Control	-	-	-	-	-
Diabetic Control	-	-	> 800	-	-
Metformin	20.35	12.16	> 800	399	49.88
Extract (200 mg/kg bwt)	12.26	7.87	> 800	421	52.63
Extract (300 mg/kg bwt)	29.08	17.02	364	227	62.36

Data are weight and FBG parameters and are expressed as mean ± SEM (n = 5).

Table 2: Comparison of Organ and Relative Organ Weights

Group	Weight of Heart (g)	Organ/Body Weight Ratio x 10 ⁻³
Normal Control	0.56 ± 0.04	3.03 ± 0.26
Diabetic Control	0.47 ± 0.06 ^a	2.89 ± 0.15 ^a
Metformin	0.52 ± 0.04 ^b	3.54 ± 0.09 ^b
Extract (200 mg/kg bwt)	0.54 ± 0.04 ^b	3.21 ± 0.24 ^b
Extract (300 mg/kg bwt)	0.64 ± 0.05 ^b	4.51 ± 0.52 ^b

Data are Weights of rat organs and are expressed as mean ± SEM (n = 5)

Values with superscript “a” are significantly different from the normal control group.

Values with superscript “b” are significantly different from the diabetic control group.

Cardiac Oxidative Status in Diabetic Rats

Induction of diabetes mellitus with STZ markedly reduced the activities of the markers of oxidative stress and NO level in cardiac tissue (p < 0.05). However, treatment of diabetic rats with ethanol extract of *C. sativus* significantly increased the activities of the

antioxidant enzymes as well as NO level (p < 0.05), but it did not significantly alter cardiac TP (p > 0.05). These results are shown in Tables 3 to 6.

Table 3: Effect of *C. sativus* Fruit Extract on Cardiac TP and MDA Level

Group	TP (g/dL)	MDA (mole/mg tissue) x 10 ⁻⁵
Normal Control	9.09 ± 0.52	1.16 ± 0.07
Diabetic Control	6.76 ± 0.09	3.90 ± 0.22 ^a
Metformin	6.29 ± 0.71	1.22 ± 0.41 ^b
Extract (200 mg/kg bwt)	10.26 ± 0.83	1.49 ± 0.11 ^b
Extract (300 mg/kg bwt)	10.02 ± 0.75	0.64 ± 0.04 ^b

Data are cardiac TP and MDA concentration, and are expressed as mean ± standard error of mean (SEM, n = 5)

Values with superscript “a” are significantly different from the normal control group.

Values with superscript “b” are significantly different from the diabetic control group.

Table 4: Effect of Ethanol Extract of *C. sativus* on Cardiac Oxidative Status in Diabetic Rats

Group	Catalase (unit/min) x 10 ⁻²	SOD (unit/min) x 10 ⁻⁴	GPx (unit/min) x 10 ⁻⁴
Normal Control	7.43 ± 0.61	11.47 ± 1.05	14.99 ± 1.20
Diabetic Control	3.84 ± 0.59 ^a	5.11 ± 0.19 ^a	9.66 ± 0.00 ^a
Metformin	6.94 ± 0.57 ^b	14.53 ± 1.01 ^b	18.54 ± 1.72 ^b
Extract (200 mg/kg bwt)	3.59 ± 0.11	14.44 ± 1.31 ^b	13.34 ± 0.92 ^b
Extract (300 mg/kg bwt)	4.95 ± 0.09 ^b	15.44 ± 1.09 ^b	10.55 ± 0.00 ^b

Data are cardiac oxidative status and are expressed as mean ± SEM (n = 5)
 Values with superscript “a” are significantly different from the normal control group.
 Values with superscript “b” are significantly different from the diabetic control group.

Table 5: Effect of Ethanol Extract of *C. sativus* on Glutathione Level

Group	GR (unit/min) x 10 ⁻¹	GSH (mg/dL)	% GSH
Normal Control	7.52 ± 0.51	36.27 ± 0.00	92.92 ± 1.08
Diabetic Control	5.96 ± 0.09 ^a	11.92 ± 0.00 ^a	76.67 ± 0.83 ^a
Metformin	33.17 ± 1.17 ^b	66.33 ± 0.00 ^b	94.58 ± 0.00 ^b
Extract (200 mg/kg bwt)	14.51 ± 0.83 ^b	15.03 ± 0.00 ^b	89.59 ± 2.06 ^b
Extract (300 mg/kg bwt)	18.14 ± 0.92 ^b	29.02 ± 0.94 ^b	90.42 ± 0.00 ^b

Data are glutathione concentrations and are expressed as mean ± sem (n = 5)
 Values with superscript “a” are significantly different from the normal control group.
 Values with superscript “b” are significantly different from the diabetic control group.

Table 6: Effect of Ethanol Extract of *C. sativus* on Cardiac NO Level

Group	NO Concentration (µmole/L)	% NO
Normal Control	96.50 ± 3.10	32.28 ± 3.07
Diabetic Control	64.25 ± 1.08 ^a	18.41 ± 0.00 ^a
Metformin	83.75 ± 2.17 ^b	46.57 ± 2.16 ^b
Extract (200 mg/kg bwt)	94.00 ± 2.40 ^b	24.49 ± 1.01 ^b
Extract (300 mg/kg bwt)	92.75 ± 1.88 ^b	26.95 ± 1.84 ^b

Data are cardiac no concentrations and are expressed as mean ± sem (n = 5)
 Values with superscript “a” are significantly different from the normal control group.

Values with superscript “b” are significantly different from the diabetic control group.

Discussion

The toxicity produced by STZ impart negatively on organs such as liver, kidneys, heart and lung. The exact molecular mechanism underlying the cytotoxic effect of STZ is not well-understood, however researches suggest that the cytotoxicity could be via production of reactive oxygen species (ROS) thus inducing oxidative stress, causing DNA damage with resultant necrosis due to the DNA methylating activity of the methyl nitroso urea moiety of the drug, release of NO which inhibits aconitase activity resulting in mitochondrial dysfunction, or via inhibition of O-linked β -N-acetylglucosaminase (O-GlcNAcase) [30].

Reactive oxygen species (ROS) and oxidative stress have been shown to play an important role in the etiopathogenesis of tissue injury. The role of oxidative stress in cardiac hypertrophy and remodeling has been demonstrated. An increased generation of ROS in the vascular wall and a reduction of NO bioavailability lead to endothelial dysfunction in atherogenesis [31-32]. The ROS cause damage to cellular structures within the vascular wall, thereby triggering several redox-sensitive transcriptional pathways, shifting the cell towards a pro-atherogenic transcriptomic profile. Animal models of atherosclerosis demonstrate the involvement of ROS in atherosclerosis by the accumulation of lipid peroxidation products and induction of inflammatory genes and activation of matrix metalloproteinases [33,34]. The ROS and reactive nitrogen species (RNS) produced by the endothelium promote oxidative modification of low-density lipoprotein-cholesterol (LDL-C) in the phase that precedes the transfer into the sub-endothelial space of the arterial wall, where they initiate atherosclerosis [35].

Lipid peroxidation is known to have deleterious effects on structure and functions of cell membrane. Malondialdehyde (MDA) is an important lipid peroxidation index, as individuals affected by several diseases usually have elevated MDA levels. It arises from the breakdown of lipid peroxy radicals. Once formed, free radicals trigger a cascade of reactions that culminate in lipid peroxidation [36,37]. Catalase plays an important role in antioxidant defense system. In animals, hydrogen peroxide (H₂O₂) is detoxified by catalase and GPx. Catalase protects cells from H₂O₂ generated within them. Superoxide dismutase (SOD) catalyzes the dismutation of the highly reactive superoxide anion (O₂⁻) to O₂ and to the less reactive species H₂O₂ [37].

Plants are at the center of Traditional Medicine. Their use in disease management is as old as man. Medicinal plants serve as cheap alternative to orthodox medicine since they are readily available [38-54].

Cucurbits are vegetable crops, belonging to the family *Cucurbitaceae*, which primarily comprised species consumed as food worldwide. Cucurbits are an excellent fruit in nature having composition of all the essential constituents required for good health [55]. They are consumed as vegetables and salads because of availability at low cost. Cucumbers are botanically categorized as berries, which are available in many different sizes, shapes and colours. They range from thick, stubby little fruits (10-12 cm long) to Dutch greenhouse varieties (of up to 50 cm long) [55]. The most popular variety is the long smooth salad cucumber which has a smooth, dark-green skin. Its little brother, the "gherkin" is actually a cucumber that has been harvested when little and pickled in brine. The parts of this medicinal plant which are traditionally used are leaves, flowers, seeds, fruits, and

bark. These parts contain bioactive compounds responsible for particular pharmacological activity [56]. *Cucumis sativus* is used in traditional medicine for the treatment of various ailments [57].

In the present study, induction of diabetes mellitus with STZ markedly reduced the activities of the markers of oxidative stress and NO level in cardiac tissue. However, treatment of diabetic rats with ethanol extract of *C. sativus* significantly increased the activities of the antioxidant enzymes as well as NO level, but it did not significantly alter cardiac TP concentration. These results are in conformity with reports of previous studies [58-61]. The cardioprotective effect of medicinal plants may involve attenuation of the damage in cardiac muscle cells, vascular smooth muscle cells (VSMCs), endothelial cells (ECs), and macrophages and monocytes. In cardiomyocytes, cardioprotective agents may promote the opening of K_{ATP} channel, increased secretion of atrial natriuretic peptide, as well as the regulation of cardiac hypertrophy, oxidative stress, and apoptosis [62, 63].

Conclusion

The results of this study indicate that ethanol extract of *C. sativus* enhance antioxidant defense in rat heart exposed to STZ. Its bioactive molecules may exert cardioprotective function via suppression of specific factors, regulation of key enzymes, and scavenging of oxygen-free radicals.

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