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Antioxidant Activity of *Passiflora foetida* Leaf Extracts and Silver Nanoparticles in Diabetic Induced Rats

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Abstract

The anti-oxidant system present in our body prevents against the free radicals. Anti-oxidants were glutathione peroxidise, serum catalase, vitamin E, ascorbic acid and superoxide. In our study the plant extract of Passiflora foetidae were used to estimate the antioxidant levels in diet-induced diabetic rats. The mean of glutathione peroxide of normal rats was 92.98±1.65. "The mean of diet-induced diabetic rats was 152.50 ± 1.92. Diabetic rats treated with sitagliptin and vildagliptin had mean values of 121.75 ± 4.33* and 124.90 ± 2.85*, respectively. The mean values of Ascorbic acid in normal rats was 0.50±0.27. Diet-induced diabetic rats have ascorbic acid mean 3.50±0.28. The normal rat's mean of serum catalase was 112.55±1.76. Diet induced rats have mean a value of 125.78±1.96*. This value is significant. Diet-induced diabetic rats treated with a standard drug have a mean of 121.38 ± 1.68*. Diabetic rats treated with plant extracts of PSF (Passiflora foetida leaf) exhibit mean values of 123.47 ± 1.67*, 119.27 ± 4.38*, and 113.07 ± 3.82. The outcomes of our study indicate that both plant extracts and standard drugs improve the anti-oxidant levels.*

Keywords: Anti-oxidants, ascorbic acid, glutathione peroxidase, serum catalase, plant extracts.

INTRODUCTION

Humans have evolved with antioxidant systems to protect against free radicals. These systems include some antioxidants produced in the body (endogenous) and others obtained from the diet (exogenous). The endogenous antioxidants consist of enzymatic defenses such as glutathione peroxidase, catalase, and superoxide dismutase. These enzymes metabolize superoxide, hydrogen peroxide, and lipid peroxides, thus preventing the formation of toxic substances. Additionally, nonenzymatic defenses like glutathione, histidine-peptides, iron-binding proteins such as transferrin and ferritin, dihydrolipoic acid, melatonin, urate, and plasma protein thiols contribute to this protective system.

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Medicinal plants play a pivotal role in the healthcare of ancient and modern cultures. Ayurveda, the Indian system of medicine, primarily utilizes plant-based drugs or formulations to treat various human ailments due to their rich therapeutic components [1]. In addition, plant based drugs remain an important source of therapeutic agents because of the availability, relatively cheaper cost and non-toxic nature when compared to modern medicine [2, 3]. Many herbs contain antioxidant compounds that protect cells against the damaging effects of reactive oxygen species (ROS). ROS, such as superoxide anion, hydroxyl radical, and hydrogen

peroxide, play a crucial role in the development of various ailments, such as arthritis, asthma, dementia, mongolism, carcinoma, and Parkinson's disease. Free radicals in the human body are generated through aerobic respiration or from exogenous sources [4, 5]. Some of the in-vivo free radicals play a positive role in processes such as phagocytosis, energy production, and regulation of cell growth. However, free radicals can also be harmful. Those produced in the body react with various biological molecules, including lipids, proteins, and deoxyribonucleic acids, leading to an imbalance between oxidants and antioxidants. Although our body has a natural antioxidant defense system, there is an ongoing need for antioxidants from natural sources [6]. Phenolic compounds from medicinal plants possess strong antioxidant activity and may help to protect the cells against the oxidative damage caused by free-radicals [7]. They are well known as radical scavengers, metal chelators, reducing agents, hydrogen donors, and singlet oxygen quenchers [8, 9]. Antioxidants from plant materials terminate the action of free radicals thereby protecting the body from various diseases [10]. There is a growing interest all over the world for discovering the untapped reservoir of medicinal plants.

Glutathione (GSH) is the primary intracellular free radical scavenger, playing a crucial role in maintaining plasma antioxidant status. It serves as a cofactor for several enzymes and contains a free thiol group capable of forming disulfide bonds with other GSH molecules or thiol-containing compounds. The balance between reduced and oxidized GSH levels inside cells reflects the cellular redox status. GSH is synthesized in two steps using the amino acids glycine, cysteine, and glutamate. Additionally, it acts as a cofactor for various antioxidant enzymes, including GSH peroxidase, GSH reductase, and GSH-S-transferase. Levels of reduced glutathione have been shown to decrease in many models of diabetes/ hyperglycemia and in diabetic patients. Reduced glutathione is decreased in erythrocytes [11, 12], retina [13], and kidneys [14] of STZ-induced diabetic rats and in the liver and endothelial cells from alloxan-induced diabetic rabbits [15]. Reduced glutathione is also depleted in erythrocytes [16], reticulocytes [17], and platelets [18] from NIDDM patients and erythrocytes [19], mononuclear leukocytes [20], and polymorphonuclear leukocytes from IDDM patients [21]. The loss of reduced glutathione may be due to a drop in activity of glutamyl-cysteine synthetase, the rate limiting enzyme in the synthesis of glutathione, and to an increase in oxidation.The present study was undertaken to investigate the effect of *Passiflorafoetida*(PSF)extract on antioxidant defence system in diet induced diabetic rats.

Vitamin C is a major hydrophilic antioxidant in both plasma and the cytosol of many cells. Vitamin C contributes to the neutralization of many water-soluble oxidants and acts synergistically with vitamin E to terminate radical induced lipid oxidation. Vitamin C levels are reduced in plasma from patients with NIDDM and metabolic syndrome [22], and in the plasma, liver, and kidneys of STZ-induced diabetic rats. The amount of vitamin C present in the plasma is inversely related to the duration of NIDDM. Treatment of diabetic rats with the antioxidant α-lipoic acid or insulin partially suppresses the loss of vitamin C in the plasma, liver, and kidney, indicating the importance of overall antioxidant status and glycemic control in the maintenance of vitamin C levels [23].

MATERIALS AND METHODS

Animal Material

Sprague dawly rats weighing (200 to 300) were used in this study, purchased from Mahaveer enterprises, Hyderabad.

Inducing Diet Diabetes Procedure

Diabetes was induced by exposing Sprague Dawley rats to a high-fat, high-carbohydrate diet for 20 weeks. The high-fat diet (HFD) used was Harlan Teklad formula TD93075, which contained 55% of calories from fat. The animals were then randomized into 9 groups, each consisting of 5 animals.

Experimental Groups

G1: Normal animals (non diabetic)
G2: Diet induced diabetic animals (DID animals)
G3: DID animals+ Glipizid (referent antidiabetic drug) 4 mg/kg
G4: DID+ ethanolic extract of *passiflora foetida* 100 mg/kg
G5: DID+ ethanolic extract of *passiflora foetida* 250 mg/kg
G6: DID+ ethanolic extract of *passiflora foetida* 500 mg/kg
G7: DID+ Sitagliptin 0.28 mg/200 g (hypoglycemic drug)
G8: DID+ Vildagliptin 10 mg/kg (hypoglycemic drug)
G9: DID+ silver nanoparticles (50 ug) 2 ml/200 gms

Estimation of Glutathione Peroxidase

The activity of GPx in the erythrocytes and tissues was measured by the method of . A known amount of enzyme preparation was allowed to react with H_2O_2 in the presence of GSH for a specified time period. Then the remaining GSH content was measured.

Tissue was homogenized in this buffer. To 0.2 mL of this, EDTA, sodium azide, and tissue homogenate (0.2 mL, 0.1 mL, and 0.5 mL, respectively) were added. Next, GSH (0.2 mL) and H2O2 (0.1 mL) were introduced, followed by mixing and incubation at 37°C for 10 minutes. A control lacking homogenate was also prepared. After incubation, the reaction was stopped with 0.5 mL of 10% TCA, followed by centrifugation. The resulting supernatant was used to assay GSH content [24]. The activity was expressed as μg of GSH utilized/min/mg of protein for tissues or μg of GSH utilized/min/mg of Hb for erythrocytes.

Estimation of Catalase

The activity of catalase in the erythrocytes and tissues was determined by the method of Sinha [25]. Dichromate in acetic acid underwent conversion to perchromic acid and subsequently to chromic acetate upon heating with H_2O_2. The resulting chromic acetate was quantified at 620 nm. Catalase samples were exposed to H_2O_2 for varying durations. The reaction was halted at specific intervals by introducing a dichromate-acetic acid solution, and the remaining H_2O_2 was determined colorimetrically as chromic acetate.

In the procedure, tissue homogenate was prepared using 0.01 M phosphate buffer (pH 7.0). To 0.9 ml of phosphate buffer, 0.1 ml of tissue homogenate (or 0.1 ml of serum) and 0.4 ml of hydrogen peroxide were added. The reaction was stopped at 30-second intervals by adding 2.0 ml of dichromate-acetic acid mixture. Tubes were then placed in a boiling water bath for 10 minutes, cooled, and the resulting color was measured at 620 nm. Standards ranging from 20-100 μ /mol were used for calibration. Specific activity was expressed as μ /mol of H_2O_2 consumed/min/mg of protein for tissues or μ /mol of H_2O_2 consumed/min/mg of Hb for erythrocytes.

Estimation of Ascorbic acid (Vitamin C)

The levels of ascorbic acid in plasma, erythrocytes, and tissues were determined using the method of Roe and Kuether [26]. Ascorbic acid was converted to dehydroascorbic acid without mixing, then coupled with 2,4-dinitrophenylhydrazine (DNPH) in the presence of thiourea as a mild reducing agent. The resulting dinitrophenylhydrazone compound developed a red color when treated with sulfuric acid, which was measured at 540 nm using a Spectronic 20.

To analyze the samples, 0.5 mL of each was mixed with 1.5 mL of 6% TCA, left to stand for 5 minutes, and then centrifuged. The resulting supernatant was filtered after adding 0.3 g of acid-washed, converting ascorbic acid to dehydroascorbic acid. Next, 2 mL of the filtrate was combined with 0.5 mL of DNPH, sealed, and incubated in a 37°C water bath for precisely 3 hours. After cooling in ice water, 2.5 mL of 85% sulfuric acid was added dropwise. The mixtures were then left at room temperature for 30 minutes. Standard solutions (20–100 μg of ascorbic acid) were treated similarly,

including a blank with 2.0 mL of 4% TCA. The resulting color was measured at 540 nm using a Spectronic 20 spectrophotometer. The results were expressed as mg/dL for plasma, μg/mg of protein for tissues, or μg/mg of Hb for erythrocytes.

RESULTS

Glutathione Peroxidase

Numeric values presented in Table 1 show that the normal activity of glutathione peroxidase in normal blood is about (92.98±1.65) but the diet induced diabetes increases significantly this parameter to a level of (152.50±1.92*), all antihyperglycemic reference drugs decreased significantly the increase glutathione peroxidase induced by diabetes into (124.70±1.96*), (121.75±4.33*) and (124.90±2.85*) respectively in Glipizide, Sitagliptin and Vildagliptin diabetic treated groups. Silver nanoparticles were also capable of decreasing the parameter described into (135.28±2.34*).

The effect of plant extract treatment was clearly presented in the table below, it decreases significantly the activity of glutathione peroxidase, (127.37±1.86*) and (126.42±3.23*) are the values of glutathione peroxidase activity in *Passiflora foetida* 100 and 250mg/kg treated diabetic groups. The high dose of studied extract 500 mg/kg was the most effective treatment that decrease highly significantly and normalize the glutathione peroxidase (93.77±2.56*).

Serum Catalase Levels

Diabetes pathology is responsible of the increase of serum catalase levels which reach (125.78±1.96*) in comparison with the normal group levels (112.55±1.76*). Hypoglycemic drugs increased these levels in order of (124.70±1.96), (117.23±2.78), (117.25±2.53) and 135.28±2.34 respectively in Glipizide, Sitagliptin, Vildagliptin and Silver nanoparticle diabetic treated groups. The high dose (500 mg/kg) of passiflora foetida ethanolic extract prove again its efficiency to correct the serum catalase levels which return to (113.07±3.82).

Ascorbic Acid

Its normal concentration in normal animals is about (0.50±0.27), diet induced diabetic rats have shown a significantly increase in this parameter (3.50±0.28). All antihyperglycemic drugs and plant treatment decreased significantly the concentration of ascorbic acid. 500 mg/kg of ethanolic extract of *Passiflora foetida* is responsible of the stabilization of this parameter and its correction to a value of (0.54±0.11).

DISCUSSION

Results of the current study show the potential antioxidant activity of *passiflora foetida* ehtanolic extract in diet induced diabetic rats [27]. This extract is more effective when administrated in a high dose (500mg/kg), it's responsible of the correction of peroxidase glutathione, serum catalase levels and ascorbic acid in diabetic animals.

Earlier studies have demonstrated the presence of polyphenols, tannins and flavonoids in ethanolic extract of *Passiflora foetida*, these chemical compounds are known by their important antioxidant power [27, 28].

Table 1. Glutathione peroxidase, serum catalase and Ascorbic acid levels in experimental groups.

	Glutathione peroxidase	Serum catalase levels	Ascorbic acid
Normal	92.98±1.65	112.55±1.76	0.50±0.27
DID	152.50±1.92*	125.78±1.96*	3.50±0.28*
Standard Glipizide-4 mg/kg	124.70±1.96*	121.38±1.68*	2.00±0.42*
Plant extract 100mg/kg	127.37±1.86*	123.47±1.67*	2.89±1.13*
Plant extract 250mg/kg	126.42±3.23*	119.27±4.38*	2.37±0.73*
Plant extract 500mg/kg	93.77±2.56	113.07±3.82	0.54±0.11

Sitagliptin-0.28mg/200grams body weight	121.75±4.33*	117.23±2.78*	1.41±0.22*
Vildagliptin-10mg/kg body weight	124.90±2.85*	117.25±2.53*	1.50±0.18*
Silver nano particles(50ug)-2 ml/200gms body weight	135.28±2.34*	114.42±2.63	3.30±0.21*

Flavonoids, abundant in vegetables, fruits, grains, and tea, are natural polyphenols crucial for various plant biological processes and environmental responses. These plant secondary metabolites are prevalent in human diets, offering antioxidant effects and diverse bioactivities [12, 27, 29].

Flavonoids are integral to numerous nutraceutical products, showcasing significant biological activity primarily centered on their well-documented antioxidant properties. This antioxidant function entails several mechanisms, including scavenging of reactive oxygen species (ROS), activation of antioxidant enzymes, inhibition of oxidases such as xanthine oxidase (XO), cyclooxygenase (COX), lipoxygenase, and phosphoinositide 3-kinase (PI3K), along with the reduction of α-tocopheryl radicals. Moreover, flavonoids are known to elevate uric acid levels, exhibit metal-chelating capabilities, and demonstrate low molecular-weight antioxidant activity, collectively mitigating oxidative stress [30–35].

A high ingestion of flavonoids from fresh fruits and vegetables may offer defense against oxidation, inflammation, and chronic diseases. Various small dietary intervention trials suggest that consuming flavonoid-rich foods might shield against the advancement of insulin resistance to type 2 diabetes by modulating pancreatic β-cell, hepatocyte, and adipocyte function [36]. The intake of specific flavonoids as quercetin was found to be inversely associated with the risk of type 2 diabetes development.

CONCLUSION

The present study showed various values of antioxidant levels with different standard drugs. Glutathione peroxidase, serum catalase, and ascorbic acid levels increase with low, medium, and high doses of plant extractsThe standard drugs are also showed maximum antioxidant levels when compared to normal rats. The drugs sitagliptin, vildagliptin and silver nanoparticles have higher level of antioxidant activity. The plant extract of high dose has low level of antioxidant activity. This shows Passiflora foetida extracts and standard drugs used in the experiments have antioxidant activity and improve the antioxidant activity when compared to normal rats.

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