Egyptian *Physalis peruviana* L. as Anti-diabetic and Hypolipidemic Natural Herb: A Promising Treatment of Alloxan-Induced Diabetic Rats

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Abstract
Diabetes mellitus and associated complications continue to be a major health concern. The estimated number of diabetic patients is increasing worldwide despite new medicine discoveries. It is likely to increase to over 300 million by the year 2025. According to IDF diabetes Atlas 2015, an adult with diabetes in Egypt reaches 8.1 million. Due to the side effects of synthetic anti-diabetic drugs, the search for safe and effective anti-diabetic agents continues to be an important area of research. Physalis peruviana Linn. (Family Solanaceae) commonly called "Harankash" in Egypt is a small tropical annual herb. It is used in ethnomedicine for treating malaria, asthma and hepatitis. We aimed to investigate possible anti-diabetic, hypo-lipidaemic and antioxidant effects of Physalis peruviana on experimentally alloxan-induced diabetes mellitus. Thirty-five rats were divided into 5 groups [(7 rats/group]: Normal &6 diabetics groups with different treatments; treatments: Non, glibenclamide, dried physalis, physalis p. ethanolic extract). The experiment lasted for 6 weeks. Fasting blood serum was analysed for blood glucose, cholesterol, HDL-C, LDL-C and triacylglycerol levels. Also HbA1c and MDA were analyzed. Dried physalis powder or its ethanolic extract was significantly effective in lowering serum glucose, cholesterol and triacylglycerol levels in the dried physalis powder or its ethanolic extract -treated diabetic rats compared with the control diabetic rats which exhibit hyperglycaemia accompanied with weight loss. Also increase HDL-C level, returning to near normal level. The present results indicate that dried physalis powder or its ethanolic extract possesses hypoglycemia, hypocholesterolemic and hypolipidaemic potential.
Keywords: *Physalis puryviana L, Antidiabetic drugs, Hyperlipidemia,*

Introduction

Diabetes is the most known metabolic disorder characterized by high level of blood glucose resulting from defects concerning insulin secretion, insulin action, or both **(1)** and results in impaired function in carbohydrate, lipid and protein metabolism**.** Type II diabetes accounts for >90% of diabetes. There are many different reports about the prevalence of diabetes in the world. According to the International Diabetes Federation's **(2)**, Diabetes Atlas 91% of adults in high - income countries and 75% of low- and middle-income countries have Type II diabetes; while WHO stated that the number of diabetics increased from 108 million in 1985 to 422 million by 2016 which is predicted to be doubled by 2030 (World Health Organization,(**3),** while **(4)** stated that the prevalence of diabetes was estimated to increase globally to 592 million by 2035**.** In 2015, the International Diabetes Federation's **(IDF)** estimated that 193 million people with diabetes are undiagnosed and are at risk of developing complications. According to IDF diabetes Atlas 2015, an adult with diabetes in Egypt reaches 8.1 million. The prevalence of diabetes mellitus has reached epidemic proportions. The global prevalence of all age groups was estimated to be 4.4% in 2030 (**5).**

Approximately 416 million adults (around 20-79 years) were living with diabetes; estimated to grow 595 million by 2035. Majority of people with diabetes were between 40 and 59 years of age. 256 million people with diabetes were undiagnosed and 4.5 million people died due to diabetes. More than 1,106,500 children were living with insulin-dependent diabetes (type I diabetes). According to International Diabetes Federation 352 million people were at risk of developing type 2 diabetes **(2).**

Oral antidiabetic drugs include the use of the sulfonyl urea (1st & 2nd generation) derivatives like glibenclamide and Meglitinides as insulin-releasing agents; biguanide derivatives like metformin acting mainly by decreasing hepatic glucose output and increase insulin sensitivity; thiazolidinediones which increase insulin sensitivity; α-glucosidase enzyme inhibitors like acarbose to reduce sugar absorption; and new incretin as glucagon-like peptide (GLP)-1, and Dipeptidyl peptidase-IV inhibitors (DPPI-IV e.g. saxagliptin) that suppress the degradation of many peptides, including GLP-1 **(7)**.

Herbal medicine is still the most common source for primary health care of about 65-80% of the world's population, mainly in developing countries. Leaves, roots, seeds, fruit and bark can all be constituents of herbal medicines. Several plants (>800 plant species) are now known to have antidiabetic and

antilipidemic effects **(8 & 9)**. Plant products with antidiabetic activity are cheaper, more available and have lesser side effect than medicine.

The medicinal values of these plants lie in their phytochemical components which produce definite physiological actions on the human body. The most important of these components are alkaloids, tannins, flavonoids and phenolic compounds **(10).**

Of these plants is *Physalis puryviana* Linn. (Family Solanaceae) which is commonly called "*Harankash"* in Egypt, is a small tropical annual herb. It is used in ethnomedicine for treating malaria, asthma, hepatitis, dermatitis and rheumatoid arthritis **(11)**.

Physalis peruviana L, (native to the Andes) has been grown in Egypt, South Africa, India, New Zealand, Australia, and Great Britain **()**. *P. peruviana L* is a cherry-sized, yellow-fleshed berry. The round orange fruit is loosely enclosed in a papery husk, which provides a natural wrapper for storing.

We aimed at studying Egyptian *Physalis peruviana* L. as anti-diabetic and hypolipidemic natural herb as a promising treatment of alloxan-induced diabetic rats

Materials and Methods

Nutritive value of Husk tomato

Nutritive value of *Physalis puryviana* L. (Husk tomato) was chemically investigated according to **12; 13& 14)** for their protein, fat, ash, moisture, total dietary fiber and Vitamin C content. Also they were subjected to microbiological **(15)** and Aflatoxin analysis before introducing in the diet **(16;17;18).**

Preparation of *Physalis* Fruit (Fresh and Ethanol Extract)

The fruit *Physalis peruviana* L. was purchased from the local market, Cairo, Egypt. The fruit was dehusked and washed, and uniform fruits without defects were selected. *Physalis* fruit was washed with water, crushed and dried in air oven at < 50 ºC then grinded in a blender to a powder. Physalis powder was added in the basal diet as 10 %. Ethanol extract was prepared by soaking drying powder in distilled ethanol for 1 week at room temperature (with slowly rotated during this time). Ethanol extract was filtered by cotton wool. Extract was dried on a rotary evaporator (Buchi) at 40°C. The residues were re-extracted 3 times under the same conditions **(19).** The 100 gm of dried powder of Physalis *peruviana* L. yields 21.5 g. *Physalis* extract was dissolved in normal saline and given to rats at a dose equal to 10% as in diet by oral intubations.

Phytochemical Screening and Determination of Phenols and Flavonoids

The crude ethanolic extract of the fruit was subjected to qualitative chemical screening for the identification of the various major classes of active chemical constituents such as phenols, flavonoids, glycosides, phytosterols, saponins, tannins, and alkaloids using standard procedures of analysis **(20 & 21)**. The quantity of extract total phenolic compounds was determined using a colorimetric method with Folin-Ciocalteu reagent **(22)** and was expressed as milligrams of gallic acid equivalent per gram of dry weight (mg GAE/g DW). The total flavonoid compounds in the extract were estimated using a colorimetric method (**23**) and were calculated as quercetin equivalents (mg QE/g). All analyses were run in triplicate.

Experimental protocol

Acute Toxicity Study

Thirty-six albino rats of both sexes were divided into six groups. Groups 2-6 were treated with oral doses of 200, 400, 800, 1000, & 2000 mg/kg of the extract respectively. Group 1 was given distilled water (10ml/kg) orally. The animals were then observed for toxic symptoms and mortality for 24 hours post administration, then every day for 2 weeks.

Induction of Diabetes Mellitus in the Rats

Diabetes was introduced in rats by single intraperitoneal injection of alloxan (150 mg/kg B W, **24**). Diabetes mellitus was confirmed after 48-72 hours and only those rats with a blood glucose level of 250 mg/dl or greater were considered as diabetic rats and will be included in the study **(25).** The rats were given 5% glucose solution after 6 hrs of alloxan injection to drink water to counter hypoglycemic shock. The blood glucose levels were measured with glucometer Bioniem GM300 from the blood taken from the rats tail.

Experimental Procedures

All rats were housed individually in wire mesh cages to facilitate weighing of rats and their diet. The animals were fed on a standard rat diet for 10 days for acclimatization. The standard control rat diet **(**AIN-93 M diet formulated for adult rodents) was prepared according **to the National Research Council (26) and 27).**

Thirty-five (35) male rats, 3 months old, weighing 155-175 g will be included in the experiment. The experimental animals will be divided into 5 groups (7rats/group):

1. Group 1: Control (normal) fed on normal control diet
2. Group 2: diabetic rats not treated
3. Group 3: diabetic rats treated with antidiabetic drug as glibenclamide at a dose of 10 mg/kg BW.
4. Group 4: diabetic rats fed on control diet supplemented with powder of Physalis 10% of the diet.
5. Group 5: diabetic rats feed on an extract of Physalis (equivalent to the 10% dried powder of Physalis of the diet).

Rats" diet and body weights were also recorded on a weekly basis. Rat diet and water were given ad libitum. Initial & final body weight was recorded (IBW, FBW). Body weight gain (BWG) was calculated as follows: BWG=FBW-IBW.

The experiment lasted for 6 weeks. After the end of the experiment, rats were fasted overnight, then scarified under ether anesthesia (Sigma, USA). Fasting blood samples were taken from a hepatic portal vein, collected in tubes (plain and coated with anticoagulant). Plain tubes centrifuged for separation of serum at 3,000 rpm for 15 minutes, and sera were stored at –20 ºC for determination of the following biochemical measurements; Glucose, total cholesterol, HDL-C, LDL-C, VLDL-C, and triacylglycerol. One EDTA tubes were centrifuged at 3,000 rpm for 15 minutes to get plasma for the determination of malondialdehyde, HbA1C was determined in the other EDTA tubes (whole blood).

Glucose was determined using Randox kit **(28). HbA1C** was determined in using Stanbio kits procedure No. 0350 (Stanbio Laboratory, Boerne, Texas; DN: RBR.0350CE.00) according 29**.** Total cholesterol, **TC,** was determined using Bio Mérieux kit (**30).** Total triacylglycerol, **TG**, was determined using Bicon kit **(31; 32).** Serum **HDL-C** was determined using Bio Mérieux kit **(33,34).** Serum **LDL-C** was determined using Bio Mérieux kit **(35).** VLDL-C was determined by using the following equation: VLDLC= total cholesterol- (HDL-C+LDL-C). **Atherogenic Index** (AI) was calculated according to **(36)** using the following equation: AI= (Total cholesterol-HDL-C)/HDL-C. Determination of Malonaldehyde Precursor by thiobarbiturateacid test: by **37.**

Glucose in urine was analyzed using glucose strips (Medi test strips, glucose-ketone; Machery – Nagel, Germany)

Fasting serum/plasma insulin level was measured using the ultrasensitive rat insulin ELISA (Thermo Scientific kits, ERINS). Determination of insulin resistance by the homeostasis model assessment – insulin resistance (HOMA-IR) and HOMA-β cell calculated as the following formula:

HOMA–IR = (fasting insulin in mIU/l X fasting glucose mmol/l)/22.5.

HOMA1-%B = (20 x fasting serum insulin (µIU/l)] / [fasting serum glucose (mmol/l) -3.5)

HOMA1 %S was calculated by reciprocal of HOMA1-IR multiplied by 100%(**38; 39; 40)**.

Statistical Analysis:

Data were expressed as means ± SEM for control and experimental animals. The data were analyzed using one-way analysis of variance (ANOVA) followed by post hock Duncan's test using SPSS v 11 (statistical package for social sciences). Also Spearman correlation was estimated using SPSS vs 11. $P < 0.05$ was used as a level of significance **(41).**

Results and Discussion

The used *Physalis peruviana* fruits were found to be aflatoxin-free and no microbial contamination were found. *Physalis peruviana* fruits were found to be non-toxic up to 2 g/kg B.W. which agree with (**42)** where no death was observed 24 hours after the oral administration of different doses of PPL on both sexes of rats although they used up to 5000 mg/ kg lyophilized fruit juice of PPL.

1-Mechanisms of alloxan-induced diabetes

Alloxan generates oxidant free radicals in a cyclic redox reaction with its reduction product, dialuric acid. Autoxidation of dialuric acid generates superoxide radicals, hydrogen peroxide and hydroxyl radicals. These hydroxyl radicals are responsible for the death of the β-cells of pancreas; triggers direct effect on islet cell permeability and inhibit glucose-stimulated insulin release at the site of hexose transport (**43;44; 45).**

2-Mechanism of Glibenclamide (Sulphonylureas) action

The sulphonylureas act to enhance the sensitivity of the β-cell to glucose and, when bound to the transmembrane sulphonylurea receptor (SUR-1), mediate the closing of the potassium-sensitive ATP channels on the cell membrane. Cellular efflux of potassium is reduced and membrane depolarisation takes place. Calcium influx is mediated by the opening of voltage-dependent Ca^{2+}-channels that promote the release of pre-formed insulin granules which lie just adjacent to the plasma membrane **(46)**

3-Nutritive value:

3-1- Macronutrients

Table 1 reveals nutritive value, minerals and vitamins content of fresh PPL. *Physalis peruviana* fruits (powder) considered a good source of nutrients and dietary fiber. The protein, fat, ash, Moisture content of PPLFP is 2.28, 0.6, 0.6, 82.16 g/100 g respectively which agree with **47 and 48** and disagree with **49** for protein; agree with **50** and disagree with **47** for fat**;** agree with **47; 49** for carbohydrate. *Physalis peruviana* fruits (powder) considered a good source of dietary fiber.

3-2-Minerals

Minerals play several important roles in human physiology and biochemistry as co-factors for enzymes, fertility, mental stability, and immunity. Table 1 presents mineral composition of Physalis peruviana L. Our study revealed that Physalis peruviana fruit contains (in mg/100gm): sodium (2.5), potassium (330) which disagree with **51** (210) since our results are much higher, Calcium (19.1), magnesium (19.0), phosphorus (51.0) which disagree with **47** (292.65), iron (1.1) which disagree with **50** (1.47), zinc (0.42) which agree with **50** (0.40), copper (031) and chromium (0.02)

3-3-Vitamins

Vitamins are important to maintain health, the growth of human being. Vitamin E and C are an important dietary antioxidant, since it reduces the adverse effects of reactive oxygen that cause damage to cells. *Physalis peruviana* fruit contain high concentration of vitamins as β-carotene (1200 mg/100g) which agree **with 48 (**1074.67 mg/100g**);** the thiamine (vitamin B1), niacin (vitamin B3), Vitamin C content of *Physalis peruviana* fruit are 0.14, 1.8 & 38.0 mg/100g which agree with **49** (0.1 & 1.7, 43.0).

Table 1: Nutritive value of Physalis

Macronutrients		Minerals		Vitamins	
Energy (cal)	**71.96**	**Na**	**2.5**	**B-carotene**	**1200**
Water (g)	**82.16**	**K**	**330.0**	**Vit C**	**38.0**
Protein (g)	**2.28**	**Ca**	**19.1**	**Vit E**	**89.1**
Fat (g)	**0.6**	**Mg**	**19.0**	**Thiamine B1**	**0.14**
Carbohydrates	**14.36**	**P**	**51.0**	**Riboflavin B2**	**0.04**
Fiber (g)	**3.1**	**Fe**	**1.1**	**Niacin B3**	**1.8**
Ash (g)	**0.6**	**Zn**	**0.42**		
Dietary fibre	**4.9**	**Cu**	**0.31**		
		Cr	**0.02**		

4-Phytochemical content; Total phenolic and flavonoid content:

Phytochemicals; the amounts of total phenols and flavonoids in the ethanol extracts of *Physalis* fruits are shown in Table 2. The bioactive components present in the fruit of *P. peruviana L.* make this to be considered as natural functional food, because of the physiological properties associated with its nutritional composition. Physalis contain: Alkaloids, Flavonoids, Saponins, Tannins, Phytosterol, Diterpenes, Triterpenoids, Glycosides, Anthraquinones, Phenols, Sterols, and Lactones. The main active constituents in the fruit of PPL. are Physalins A, B, D, F; Rutin, Myricetin, Quercetin, Kaempferol and glycosides, which showed multiple activities (**52)**

The total phenolic contents of ethanol extracts of Physais fruits was 95.8 mg gallic acid equivalent/ml extract which agree with **53** using Egyptian PPL. The total flavonoid content was 77.1 mg equivalent/ml extract.

Physalins contained in *Physalis* can increase enzyme activity Superoxide dismutase (SOD) and catalase to prevent free radicals damaging effect to pancreatic B cells **(54)**.

Table 2: Phytochemical analysis, Total phenolic and flavonoid content of *Physalis Peruviana L.* fruits extract

Phytoconstituents		Phytoconstituents	
Alkaloids	**+**	**Triterpenoids**	**-**
Flavonoids	**+**	**Glycosides**	**+**
Saponins	**+**	**Anthraquinones**	**-**
Tannins	**+**	**Phenols**	**+**
Phytosterol	**+**	**Sterols**	**+**
Diterpenes	**-**	**Lactones**	**+**
Total phenolic as gallic acid Equivalent/ml (mg GAE/ml))		**95.8**	
Total flavonoid		**77.1**	

5-Initial, final and Body Weight Gain

Table (3) shows IBW, FBW, BWG, and %BWG of the studied groups. At the beginning of the experiment no significant difference in body weights between groups was found. Diabetic (G2) group showed significant decrease in body weight gain compared with normal control group. Oral administration of *Physalis peruviana* L. fruits and its extract as well as glibenclamide to alloxan-induced diabetic rats showed significant ($p<0.05$) increase of the body weight to near normal. Groups 4 showed significant increase in body weight compared with their respective G 5 (Physalis: 32.79 vs 27.51%).

Diabetes is characterized with loss of body weight, which is due to increased muscle wasting and catabolism of structural tissue proteins due to scarcity of carbohydrate as energy source, **(55)** leading to significant reduction in the body weight gain of diabetic rats. The unavailability of glucose to the β-cells as result of insulin insufficiency may cause polyphagia and polydipsia **(56)** leading to weight loss due to excessive break down of tissue proteins**.**

A significant increase in the body weight was observed in diabetic rats administrated with Physalis peruviana L. fruits extract which could be due to the protective effect of the fruits in controlling muscle wasting and protein turn over and may also be due to the improvement in insulin secretion from the remnant pancreatic beta cells and glycemic control.

Table 3: Effect of Physalis on IBW, FBW, BWG, %BWG of the studied group

	IBW	FBW	BWG	%BWG
G1	168.71±2.13 [a]	224.86±1.44 [a]	56.14±1.45 [a]	33.36±1.19 [a]
G 2	167.71±1.25 [a]	186.00±2.42 [b]	18.29±1.96 [b]	10.90±1.16 [b]
G 3	166.29±2.16 [a]	220.14±2.34 [a]	53.86±1.77 [a]	32.45±1.26 [a]
G 4	164.57±4.26 [a]	218.29±4.09 [a]	53.71±0.92 [a]	32.79±1.11 [a]
G 5	166.71±1.71 [a]	212.57±2.15 [c]	45.86±0.74 [c]	27.51±0.41 [c]

Values in the same column with the different superscripts are significant at P < 0.001

5-Glucose / Insulin/ β-cell function

Table 4: Effect Physalis on FBlS, Insulin, HOMA-IR, HOMA-B, HOMA %S and HbA1c of the studied group

	Glucose	Glucose mmol/l	Insulin (µU/ml)	HOMA-IR	HOMA-β	HOMA-%S	HbA1c	Urine sugar
G1	94.05±1.30 [a]	5.22±0.07 [a]	12.15±0.32 [a]	2.82±0.07 [a]	143.00±7.98 [a]	35.67±1.03[a]	6.15±0.33 [a]	Nil
G2	337.42±37.26 [b]	18.73±2.07 [b]	9.29±0.29 [b]	7.77±0.99 [b]	13.43±1.73 [b]	13.94±1.45 [b]	8.83±0.31 [b]	+++
G3	137.41±6.38 [c]	7.63±0.35 [c]	10.87±0.19 [c]	3.70±0.22 [c,e]	54.58±3.83 [c]	27.59±1.53 [c,e]	7.16±0.23 [c]	Nil
G4	133.02±2.93 [c,e]	7.38±0.16 [c,e]	10.94±0.39 [c]	3.59±0.13 [c]	57.09±3.41 [c]	28.09±0.98 [c]	7.00±0.14 [c]	Nil
G5	142.96±1.35 [c,d]	7.93±0.07 [c,d]	11.01±0.10 [c]	3.88±0.04 [d,e]	49.75±1.04 [d]	25.78±0.26 [d,e]	7.23±0.07 [c]	Nil

Values in the same column with the different superscripts are significant at P < 0.001

Table 4-a: Correlation Coefficient

	HOMA_IR & HOMA-B		HOM-IR & AI	
	r	p	r	p
1	0.199	0.05	0.658	0.001
2	-0.760	0.005	0.287	.049
3	-0.882	0.005	0.725	0.001
4	0.223	.049	-0.573	0.005
5	-0.220	0.049	0.185	0.05

Glucose

Table (4) reveals glucose/ insulin concentration and β-cell function **Glucose** level was significantly increased ($P < 0.05$) in alloxan-induced diabetic rats compared to normal control one. The daily administration of phasalis or their extracts or antidiabetic drug to alloxan-induced diabetic rats reduces glucose level significantly although they still significantly higher than normal control group. The decrease in glucose level being more in physalis groups than their respective extract (133.02 vs 142.96 mg% respectively). Our results agree with **57.** It also agrees with **58.**

The increase in glucose level may be due to the inhibition of glycogen phosphorylase enzyme which catalyzes glycogenolysis leading to glucagon inhibition **(59)** or due to toxicity in pancreatic cells as a result of excess reactive oxygen species (ROS) leading to reduction of insulin synthesis and release **(57)**;

The improvement in glucose level of diabetic rats treated with **physali**s or its extract may be due to polyphenols / flavonoids content which prevents the damage and death of pancreatic β-cells and/or may be due to stimulation of the regeneration of β-cells in diabetic rats. According to **(60)** it was found that administration of polyphenols (quercetin and epicatechin) to diabetic rats protects the architecture of pancreatic β-cells, preserves the secretion of insulin and stimulates the regeneration of β-cells cells **(60)**, or may be due to vitamin C content which reduce glucose toxicity and contribute in part to the prevention of a decrease of β cell mass and insulin content. Or maybe that plasma vitamin C levels seem to play a key role in the modulation of insulin action in the diabetic patients. Vitamin C-mediated increase in insulin action is mainly due to an improvement in non-oxidative glucose metabolism. Vitamin C and E might enhance insulin release or sensitivity and might spared more pancreatic β-cells with more insulin availability. Also the hypoglycemic action of combined vitamins C and E in diabetic rats may be due to increase of antioxidant enzymes expressions and/or activities, or due to inactivation of the circulating free radicals that quench nitric oxide (NO) before it reaches pancreatic β-cells, causing damage and/or death **(61).**

Our results agree **with (62)** that vitamin C and/or vitamin E might have hypoglycemic effect. Vitamin C was reported to stimulate insulin –like mechanism. Also, vitamin E might improve glucose metabolism by muscle cells and the circulation to the islets of Langerhans and other tissues.

HbA1c

Excessive glucose (hyperglycemia) bonds irreversible with Hb forming HbA1c which represent a marker for glycemic **(63).** Results of table 4 reveal that **HbA1c** level was significantly increased ($P < 0.05$) in alloxan-induced diabetic rats compared to control one indicating poor glycemic control. The daily administration of phasalis or their extracts or antidiabetic drug to alloxan-induced diabetic rats reduces HbA1c level significantly although they still significantly higher than normal control group. The decrease in HbA1c level being more in physalis groups than their respective extract. The decrease indicates that there is reduced nonenzymatic glycation of proteins. The decrease could be attributed to the competition of vitamin C with glucose for the reaction with amino groups on the hemoglobin beta chain.

β-cell function

In our study, we evaluated degrees of insulin resistance (IR), β-cell dysfunction by homeostatic model assessment for IR (HOMA-IR) and β-cell dysfunction (HOMA-β). In the homeostasis model assessment (HOMA) insulin sensitivity is expressed as HOMA%S,

The relationship between glucose and insulin in the basal state reflects the balance between hepatic glucose output and insulin secretion, which is maintained by a feedback loop between the liver and β-cells.

PPL Fruits or its extract treatment decreases the insulin resistance, which is evident from the results of HOMA-IR, HOMA-B and HOMA-%S (table 4). Fruits extract administration augments insulin-stimulated glucose uptake into peripheral tissues. It is also evident that fruits extract acts as insulin sensitizer likely due to enhanced glucose uptake in the main target organs.

A higher HOMA-IR value indicates greater IR, and a lower HOMA-β value indicates greater β-cell dysfunction. HOMA-IR and HOMA-β were moderately negatively correlated (r = -0.76, table 4-a) in diabetic patients, that is, greater IR was correlated with less β-cell dysfunction.

Insulin level, HOMA-β and HOMA-%S in the alloxan-induced diabetic group (G2) was significantly lower than normal control group (G1), while its level In the 3rd, 4th, 5th groups which was fed on anti-diabetic drug (glibenclamide) or PPL or its extract was significantly increased at a rate close to normal but still significantly lower than normal, while HOMA-IR was the opposite, significantly higher than normal in diabetic group, and significantly lower in groups treated with glibenclamide, PPL or its fruits. These results may conclude that PPL or its extract has led to a significant improvement in HOMA β ratio, improved blood sugar and HbA1c. Our results agree with **(64)**

HOMA-IR may constitute a useful method not only for diagnosing insulin resistance, but also for follow-up during the treatment of patients **(65)**.

The protective effects of PPL or its extract against oxidative stress in alloxan-induced diabetic rats may be due to the presence of biologically active components in it. Chemical (nutritive, phytochemical) analysis of PPL revealed that it contains L-arginine which is important modulator of glucose metabolism and insulin sensitivity. L-arginine is reported to possess anti-glycation and anti-peroxidative potential in diabetes. L-arginine

is also reported to have the ability to regenerate pancreatic β-cells and reduce alloxan-induced pancreatic damage in diabetic rats **(66).** PPL analysis reveals that it contains in mg/100gm on fresh bases: Ascorbic acid 38; vitamin E 89.1, potassium 51, magnesium 19, calcium 19.1. PPL is considered a good source of vitamin C & E as evident from the analysis. Presence of vitamin C and/or E improve fasting blood sugar (FBS), HbA1c, lipid profile, insulin, homeostasis model assessment of insulin resistance (HOMA-IR) as suggested by **(67)** who found beneficial effects of supplementing antioxidant vitamins in T2DM which could improve the clinical condition and attenuate or prevent diabetic pathogenesis which could attribute to the imbalance between the decline in the endogenous antioxidants and increasing production of the reactive oxygen species leading to the oxidant-mediated damage. **(68)** found that vitamin C and/or vitamin E increases SOD activity, provides anti-inflammatory action and it can directly scavenge singlet oxygen, superoxide and hydroxyl radicals.

PPL contain K, which its serum levels might affect insulin secretion by pancreatic β-cells and dietary potassium intake is significantly associated with the risk for diabetes mellitus as suggested by **(69)**. Manganese, another important mineral present in PPL, it possesses protective effects against diabetes and activates a number of enzymes involved in antioxidant mechanisms and carbohydrate metabolism **(70)**

6-Lipid Profile

Table 5: Effect of Physalis on Lipid profile of the studied group (mg%)

	Cholesterol	HDL-C	LDL-C	VLDL-C	TRI	AI	MDA
G1	84.51±2.89^{a}	40.09±1.12^{a}	27.10±2.47^{a}	17.33±0.49^{a}	86.66±2.44^{a}	1.11±0.08^{a}	65.02±1.21^{a}
G2	181.63±2.38^{b}	36.44±1.15^{b}	119.86±2.44^{b}	25.33±0.32^{b}	126.67±1.58^{b}	4.01±0.17^{b}	106.49±4.77^{b}
G3	133.46±3.37^{c}	38.50±0.99^{a,b}	76.23±3.95^{c}	18.73±0.34^{a}	93.63±1.72^{c}	2.49±0.16^{c}	77.56±2.13^{c}
G4	139.73±2.31^{c}	40.18±0.56^{a}	82.36±2.33^{d}	17.20±0.27^{a}	85.98±1.35^{a}	2.48±0.06^{c}	74.11±1.22^{e,c}
G5	143.25±2.45^{c}	39.95±0.68^{a}	85.10±2.15^{d}	18.20±0.46^{a}	91.02±2.31^{c}	2.59±0.06^{c}	78.78±2.28^{e,c}

Values in the same column with the different superscripts are significant at P < 0.001

Diabetes / dyslipidemia is characterized by high plasma triglyceride concentration (hypertriglyceridemia), low HDL-C concentration and increased concentration of small dense LDL-C particles which are major coronary risk factors associated with uncontrolled diabetes **(71).** Cholesterol is a powerful risk factor for coronary heart diseases. The degree of hypercholesterolemia is directly proportional to the severity of diabetes.

In the present study, rats fed diet supplemented with *physalis* powder or its extract caused reduction in the elevated levels of serum cholesterol, LDL-C and triacylglycerol of diabetic rats, but HDL-C level was significantly increased when compared with the diabetic group returning to near normal (no significant change). Also, we have observed higher levels of cholesterol in the serum/plasma of diabetic rats. The increased levels of cholesterol in the plasma are due to the decreased level of HDL-C. This in turn results in decreased removal of cholesterol from the extrahepatic tissues by the HDL-C**.** This is probably due to the presence of phytosterols in the *physalis* fruit which induce a decrease in lipoprotein cholesterol levels in total plasma **(72);** or may be due to the decrease in cholesterol solubility and their absorption across the intestinal barrier, inducing consequently low plasma cholesterol levels due to presence of phytochemicals as myricetin, quercetin, kaempferol as suggested by **73 and 74**. Also **75** suggested that the hypocholesterolemic effects of PPL are mainly due to the lycopene existing in the plant which is a strong antioxidant which inhibits the production of LDL-C and presumably increases the excretion through releasing cholesterol; therefore, it reduces blood cholesterol level and controls cholesterol synthesis. These findings are in agreement with previous study conducted by **76** who suggested that PPL has been effective in reducing cholesterol level, and also agree with **77** although his study was done using PPL pomace on rats fed high cholesterol diet**.** Also**,** our results agree with **78** although their work was on hypercholesterolemic patients, and agree with **79** where they found that vitamin C improves basal metabolic rate and lipid profile in alloxan-induced diabetes mellitus in rats.

Diabetes hypertriglyceridemia may be due to impaired removal of triglyceride-rich lipoproteins, or due to increased mobilization of fatty acids from adipose tissue and/ or elevation of free fatty acid level in the blood, leading to the production of ketone bodies in the liver. Also may be due to accumulation of VLDL particles, either by overproduction or decreased catabolism or both. The elevated level of serum lipids in diabetics is due to increase in the mobilization of free fatty acids from the peripheral depots, since insulin inhibits the activity of hormone-sensitive lipase. Treatment with the *Physalis peruviana* L. fruits or its extract to diabetic rats resulted in the correction of hyperlipidemia and this may be attributed to the enhanced glucose utilization.

Atherogenic Index (AI) is inversely and significantly correlated with insulin sensitivity which agrees with **80** who reported that AI correlates with insulin resistance (HOMA- IR).

Dietary fiber

From the analysis, PPL contain a high amount of dietary fiber. **Jiang *et al.*, 81 and Tan *et al.*, 82** suggest an association between dietary fiber consumption and improved HbA1c, HDL-c, and weight levels where they found that fiber might reduce postprandial glucose, increased satiety, better glycemic control, improvement of cardiovascular risk factors, and reduced risk of macro vascular complications. Our results agree with **83** where they conclude that a higher content of fiber in the diet had an impact on reducing HbA1c and triglycerides while improving HDL-c levels. It also agrees with **84** where they stated that fiber supplementation for type 2 diabetes mellitus can beneficial in reducing fasting blood glucose and HbA1c. **Pi-Sunyer 85** stated that increased intake of total DF was inversely associated with markers of insulin resistance. **Ikem *et al.*, 86 and Ziai *et al.*, 87** stated that high fiber diet significantly reduced plasma total cholesterol concentrations and other lipid parameters except for HDL-C. The diet also induced a greater change in mean lipid parameters compared with the control group. The hypolipidemic effects of dietary fiber through binding with bile acids, thereby increasing their fecal excretion and interrupting the enterohepatic circulation of bile salts.

Conclusion

It is possible to conclude from the experimental findings that *Physalis peruviana* studied exhibited promising hypoglycaemic and hypolipidemic activity in alloxan-induced diabetic rats. It's hypoglycemic and hypolipidemic effects could represent a protective mechanism against the development of hyperglycemia and hyperlipidemia characteristic of diabetes mellitus

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