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Anti-Hyperglycemic and Antioxidant Effect of Peach (*Prunus Persica* L.) Seed Extract

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ABSTRACT

The main objective of this work is to evaluate the anti-diabetic activity and antioxidant effect of peach (*Prunus persica* L.) seed extract. In 2013, 382 million adults were diagnosed with diabetes worldwide. This number is expected to grow to 592 million in 2035. People with diabetes are at increased risk of macro -vascular and micro- vascular, as well as early mortality. In the present study adult male albino rats average (140 g) were divided into three groups: Group I: control; Group II: streptozotocin-induced diabetic; Group III: diabetic rats treated with peach seed extract, administered via an intragastric tube (0.6 ml/rat), at a dose of 150 mg/kg for 20 consecutive days after the induction of diabetes mellitus. Characterization of TBARS, carbonylated proteins, were measured in the plasma and in the supernatant of liver homogenisates, and superoxide dismutase and catalase were measured in the haemolysates of RBCs and supernatant of liver homogenisates. The results showed that oral administration of peach seed extract (150 mg/kg/day) reduced the levels of lipid peroxides and carbonylated proteins and improved the antioxidant activity in plasma and hepatic compared with the diabetic control rats. These results showed that the peach seed extract enhanced the antioxidant defense against reactive oxygen species produced under hyperglycemic conditions in diabetic adult male albino rats, also hence protecting the liver cells. Also, the results indicate that peach seed extract possessed considerable in vitro anti diabetic activity.

Keywords: Peach (*Prunus persica* L.) kernel extract, Streptozotocin induced, Antioxidant activity.

1. Introduction

According to the latest WHO data in 2020 diabetes mellitus deaths in Egypt reached 19,131 or 3.57% of total deaths. The age adjusted death rate is 27.97 per 100,000 of population ranks Egypt 92 in the world.

The International Diabetes Federation (IDF) listed Egypt among the world top 10 countries in the number of patients with diabetes. It is expected that the number of patients with diabetes in the Middle East and North Africa (MENA) region to grow by 96% from year 2013 to 2035 or from 34.6 million to 67.9 million.

In diabetes mellitus, chronic hyperglycemia produces multiple biochemical sequelae, and diabetes-induced oxidative stress could play a role in the symptoms and progression of the disease (Giugliano *et al.,* 1996). Oxidative stress may result in overproduction of oxygen free-radical precursors and/or decreased efficiency of the antioxidant system (Irina *et al.,* 2009). The oxygen free-radical generation is associated with auto-oxidation of glucose, impaired glutathione metabolism, alterations in the antioxidant enzymes and formation of lipid peroxides (Strain *et al.,* 1991). There are various endogenous defense mechanisms against free radicals, such as the enzymes GSH, SOD, GPx and CAT, whose activities eliminate superoxide, hydrogen peroxide and hydroxyl radicals (Sergent e*t al*, 2012).

In plants, flavonoids generally exist as glycosylated and sulphated derivatives (Middleton, *et al.,* 2000). Flavonoid glycosides are much more rapidly absorbed by humans (Hollman and Katan, 2003). Fruits and vegetables contain a vast array of antioxidant components, mainly polyphenols and flavonoids (Potter 1997). Flavonoids possess several physiological properties: antioxidant,

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antibacterial, antiviral, anti-inflammatory, anti-mutagenic and anti-tumor activity, as well as the activation or inactivation of certain enzymes (Rice-Evans and Packer, 2009). On the other hand, oxidative stress is increased in experimental models of streptozotocin-induced diabetes mellitus (Szkudelski, 2001) as like in diabetes disease.

Experimental and clinical studies in vitro or in vivo proved to Rutin is a polyphenolic flavonoid, which could prompt the intact functional β cells to produce insulin and or protect the functional β cells from further deterioration, which is necessary for them to remain active and to produce insulin. (Kamalakkannan *et al*., 2006 and Coskun *et al.,* 2005). Rutin supplementation decreased both the systolic and diastolic blood pressures. Rutin causes vaso-relaxation in pre-constricted endothelium-intact rings, but not in aorta rings without endothelium (Sheu, 2004).

Although the phenolic profile of the peach published by some authors (Andreotti *et al.,* 2008), there are no studies of antihyperglycemic and antioxidant effect of peach (*Prunus persica* L.) seed extract. To the best of our knowledge, no data was reported about the effect of peach (*Prunus persica* L.) seed extract on antihyperglycaemic and antioxidant activities.

Peach (*Prunus persica* L.) belongs to the Rosaceae family and is associated to stone fruits such as plums, cherries and almonds. It can be eaten either fresh or canned and its flavor can be incorporated into many beverages (Kanda *et al.,* 2012). Peaches production has an important place in the world (21.6 million tons in 2016) with a cultivated area of around 3.7 million acre. China was the first country producing peaches in the world (more than 11.9 million tons in 2016) followed by Italy (1.4 million tons) and Spain (1.3 million tons) (FAOSTAT 2016). In Egypt, the peach occupies the first place among the deciduous fruits in terms of area and economic importance, as the total area reached about 78,494 thousand acres in 2001 and its production reached about 224,183 tons according to official statistical. Egypt occupies the eleventh position among the seventeen countries that produce peaches in the world (Bulletin No. 784, 2003).

Phenolic compounds represent the main antioxidant Phytochemicals present in peaches. However, vitamin C and carotenoids also contribute to their antioxidant capacity (Cantin *et al.,*2009). Peach phenolics have been shown to display several biological activities such as antioxidant activity (Li and Wang, 2011), anti-allergic and anti-inflammatory activities, antibacterial activity (Cevallos-Casals *et al.,*2006), hepatoprotective activity, nephroprotective activity (Lee *et al*., 2009) ,antiproliferative (Geng *et al.,* 2013) , chemopreventive and anticancer activities (Heba Mohamed *et al*., 2019) and (Noratto *et al.,* 2014).

In unique study by Paulina and Aneta (2019) about bioactive compounds indentified and differentiation by (LC-MS/QT) of analysis in kernels separated from peach, which interpretation biological and physiological effect of these compounds. The LC-MS analysis of 20 different cultivars of peach kernels allowed for the identification of 18 phenolic compounds. These can be classified into three groups: flavonols and flavons, flavan-3-ols (monomer, dimers, and polymeric procyanidins) and phenolic acids (hydroxycinnamic and hydroxybenzonic acid).

During industrial processing of peaches, the kernels are usually removed and become a by-product. Considering that the peach kernels constitute from 5 to 10% of the total fruit weight, depending on the variety, ten thousands of tons of waste are generated annually, which are currently underexploited. With the increase of knowledge about the ingredients contained in kernels of stone fruit and their health-promoting potential, a great interest is aroused by the possibility of their use for human consumption, especially to enrich man's diet with compounds beneficial in the prevention of chronic diseases (Bak, 2010)

Bioactive substances of peach kernel such as phenolic compounds are antioxidants used in the food industry are essential to inhibit the formation of free radicals, preserving the existing properties in the different matrices. However, the insecurity of the synthetic antioxidants regarding human health propels search for natural substrates with potential antioxidant activity as an alternative to synthetic compounds.

On the other hand, streptozotocin is often used to induce diabetes mellitus in experimental animals through its toxic effects on pancreatic β-cells. Streptozotocin-induced diabetes mellitus is associated with the generation of reactive oxygen species causing oxidative damage (Szkudelski 2001). Diabetics and experimental animal models exhibit high oxidative stress due to persistent and chronic hyperglycemia, which thereby depletes the activity of antioxidative defense system and thus promotes *de novo* free radicals generation (Baynes and Thorpe 1997). Chemicals with antioxidant properties and

free radical scavengers may help in the regeneration of β-cells and protect pancreatic islets against the cytotoxic effects of streptozotocin (Coskun *et al.,* 2005).

Recently, searchers for appropriate hypoglycemic agents has been focused of plants used in traditional medicine partly because of leads provided by traditional medicine to natural products that may be better treatment than the currently used drugs (Rates 2001).

In turn, this study aimed to investigate (1- effect peach seed extract and ameliorate of lipid peroxidation, protein oxidation and antioxidant status in the plasma and liver of diabetic mellitus induced animals, (2- assay of their health-promoting properties, including their antioxidative properties and digestive enzymes(α Amylase, α glucosidase and pancreatic lipase) by in vitro.(to investigate the inhibitory potentials of the peach seeds extracts of on alpha amylase and alpha glucosidase, the key enzymes responsible for carbohydrate hydrolysis).

2. Material and Methods

2.1. Chemicals.

All of biochemical's were purchased from Sigma Chemical Co. (St. Louis, Mo). The chemicals were of analytical grade.

2.2. Preparation of Peach seed extract

Peach (*Prunus persica* var. *Swelling*) seeds were obtained from El-Bostan Zone, El-Beheira Governorate. Peach seeds were manually cracks, dried, and ground in a grinder into powder form. The Peach powder (yield from peach seeds was 50%). was stored at -20 ℃ until used in the experiment.

2.3. Extraction Procedures:

About 500 g of the powder was mixed with 1000 ml of 60% acetone without acidification for 180 min at 25 °C (Mokrani and Madani, 2016).The extract was then filtered through a Buchner funnel. The filtrate was evaporated at 45 °C in a rotary evaporator to concentrate the solution, then lyophilized in order to obtain the dry extract and stored at 4 °C until use.
The percentage (%) yield was calculated using the formula (Eq. 1).

Percentage Yield =Wt of the extract / Wt of the macerated sample×100……..(1)

Where, Wt = Weight in grams

2.4. Estimation of the phenolic compounds of extract:

2.4.1. Total proanthocyanidins:

Based on the procedure of (Sun *et al.,* 1998) total proanthocyanidins was determined.

The absorbance of resulting mixture was measured at 500 nm after 15 min at room temperature according. Total proanthocyanidins content was expressed as catechin equivalents (mg/g) using the following equation from the calibration curve:

$$Y = 0.5825x, R2 = 0.9277$$

Where; x was the absorbance and Y the catechin equivalent (mg/g).

2.4.2. Total flavonols and total flavonoids:

Total flavonols and total flavonoids, after 2.5 h from prepare the reacting mixture, according to method of (Ordon *et al.,* 2006) and the absorption at 420: 440 nm was read at 20°C of reacting mixture. Total flavonols and Total flavonoids content was calculated as quercetin (mg/g) equivalent from the calibration curve using the equation:

$$Y= 0.0255x, R2 = 0.9812$$

Where; x was the absorbance and Y the quercetin equivalent (mg/g).

2.4.3. Total phenol:

The total phenolic content in the peach kernel was determined spectrophotometrically with Folin Ciocalteau reagent using the modified method of (Wolfe *et al.,* 2003), and the absorbance of the samples was measured at 765 nm using Hewlett Packard, UV/visible light. Total phenolic content was expressed as mg/g tannic acid equivalent from the calibration curve using the equation:

$$Y = 0.1216x, R2 = 0.936512$$

Where; x was the absorbance and Y was the tannic acid equivalent (mg/g).

The experiment was conducted in triplicate and the results are reported as mean ± SD values.

2.5. Antioxidant activity by DPPH:

Evaluation of antioxidant activity of peach kernel extract by DPPH radical scavenging method in the prepared nutraceuticals:

Free radical scavenging activity of the prepared nutraceuticals was measured by 1,1-diphenyl-2-picryl hydrazyl (DPPH) in brief, 0.1 mM solution of DPPH in ethanol was prepared. This solution (1ml) was added to 3 ml of different nutraceuticals in ethanol at different concentrations (20, 30, 40, 50, 100, 200, 300, 400, 500 and 1000 µg/ml). The mixture was shaken vigorously and allowed to stand at room temperature for 30 min then; absorbance was measured at 517 nm by using spectrophotometer. Reference standard compound being used were BHT and ascorbic acid in different concentrations (20, 30, 40, 50, 100, 200, 300, 400,500 and 1000 µg/ml) The percent DPPH scavenging effect was calculated by using following equation: DPPH scavenging effect (%) or Percent inhibition = [A0 - A1 / A0] × 100. Where A0 was the Absorbance of control reaction and A1 was the Absorbance in presence of test or standard sample, and experiment was done in triplicate (Shekhar and Anju, 2014).

2.6. Antioxidant activity by ORAC and ABTS:

Determination of antioxidant activity by ORAC and ABTS methods, the solvent for the analysis of antioxidant activity in peach kernels was prepared according to (Wojdyło *et al*.2014) .The oxygen radical absorbance capacity (ORAC), and 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid)(ABTS) assays were prepared according to (Ou *et al.,* 2002).The antioxidant activity was expressed as mmol Trolox/100 g of peach kernels.

2.7. Inhibitory activities assays of peach kernels extract toward digestive enzymes:
α-Amylase, α-glucosidase and pancreatic lipase inhibition assays

The α-amylase and α-glucosidase inhibitory effects of the peach kernels were assayed according to (Nowicka *et al.,* 2016) while the inhibition of lipase activity was determined according to (Podsędek *et al.,* 2014), respectively. The results were expressed as IC_{50} value.

2.8. Biological evaluation:

Thirty male albino rats weighing about 140g with ages between 10 - 12 weeks (provided by the Laboratory Animal Center, Faculty of Veterinary Medicine, Cairo University) were housed in stainless steel cages in animal house Faculty of Home economics, Menofia University (Egypt), The animals were divided into two category for two major experimental, as the following:

2.9. One category, contained twelve rats for acute toxicity test:

Animals were maintained for three days prior to the experiment under standard conditions. The rats were kept without food for 3 h prior to dosing but had access to water adlibitum. Then to determine the acute toxicity study, rats were divided into 3 groups (n = 4). Group 1 and 2 , received peach kernel (PK) extract intraperitoneal in dose 200 and up to 400 mg/Kg body weight and Group 3 (control group) was receiving 1X phosphate buffer saline (PBS), after each dose, food was not provided for 2 h. Rats were critically observed for any toxic effects, including mortality after 30 min of dosing, followed by 4 h, then periodically during the first 24 h and then at regular intervals for a period of 9 days, with regular observe for external changes in eyes, skin, salivation ,heart and respiratory rate, sweating, urinary enuresis, convulsions and sleepiness were noted and record it (OECD Guideline, 2008). Weight of the rats were monitored and noted down on the 12^{th} day of study.

2.9.1. Second category, to evaluate the hypoglycemic activity of peach kernel extract, on streptozotocin-induced diabetic albino rats. Eighteen rats were divided to three groups (6 rats/group) after while being maintained in a controlled environment (12 h light and dark cycle, 22°C). During the acclimation period (1 week) and experimental period (4 weeks), the normal basal diet was supplied ad libitum. The basal diet consisted of casein 20%, corn oil 10%, cellulose (wooden fibers) 5%, salt mixture 4%, vitamin mixture 1% and starch 60% (Lane - Peter and Pearson, 1971).All experiments were conducted in accordance with Ethics of Animal experimentation (NIH, 1985).

2.9.2. Induction of experimental diabetes

Streptozotocin was freshly dissolved in citrate buffer (0.01 M, pH 4.5) and maintained on ice prior to use. Diabetes was induced with a single i.p. injection of STZ (50 mg/kg) (average 10 mg /rat) to overnight fasted rats (Kamalakkannan, 2006). Control rats were injected with citrate buffer. Diabetic status was confirmed in the STZ-treated rats by measuring the fasting plasma glucose after 72 h. Rats with plasma glucose levels (250 mg/dl) were considered diabetic (Nagasawa *et al.,* 2003).

2.10. Experimental design

Treatments with peach kernel extract were started on day 3 after STZ-injection from the acclimation period for (1 week) and experimental period (5 weeks). The normal basal diet was supplied *ad libitum*. Eight ten rats divided into three groups of 6 animals each, were used to investigate the antidiabetic and antioxidant effect of peach kernel extract as the following: Group I, non-diabetic control; Group II, diabetic control; Group III, diabetic + peach kernel extract (150 mg/kg B.W/day). The peach kernel extract was suspended in CMC (0.01 g/ml) and orally administered via an intragastric tube (21 ml/rat, per/once) on a daily basis for 35 days. Non-diabetic control and diabetic control rats received CMC alone. For each group, glucose plasma level was determined at the beginning of the experiment, 4 days after STZ administration (only for group II and group III) and at the end of the experiment rats were fasted overnight and sacrificed it by ether anesthesia 24 h after their respective 25 daily doses of the extract and distilled water , at the end of experiment and liver was eradicated, rinsed in ice cold 0.25 M sucrose solution and 10 %w/v homogenate was prepared in 0.05 M phosphate buffer (pH 7) and centrifuged at 12,000 × g for 60 min at 4°C. The supernatant obtained was used for the estimation biochemical parameters on the day of sacrifice.

2.11. Biochemical analysis:

The plasma and hepatic levels of oxidative stress were estimated, by assessing lipid peroxides and carbonylated proteins concentrations. Lipid peroxides were measured by the thiobarbituric acid reactive substances (TBARS) method (Satoh, 1978). The results were expressed in nmol MDA per mL of plasma and nmol MDA per g of tissue. Carbonylated proteins (CP) as products of the reaction between the reactive oxygen species (ROS) and proteins were determined in the plasma and hepatic tissue homogenates, using the hydrochloric guanidine method (Reznik and Packer, 1994).

The results were expressed in nmol per mg protein. The activity of superoxide dismutase (SOD) was assayed as described by (Kakkar *et al.,* 1984). A unit of the enzyme activity was defined as the enzyme reaction giving 50% inhibition of NBT reduction in 1 min under the assay conditions and expressed as specific activity in units/mg Hb, respectively units/mg protein. The Catalase (CAT) activity was assayed according to (Sinha 1972) and expressed in μmol H_2O_2 consumed/min/mg Hb, respectively units /mg protein. Glucose level was estimated using a *Glucose* (GO) *Assay Kit* (*Sigma-Aldrich* offers Sigma-AGO20).

The haemolysates was separated by centrifuging at 3000 g, for 10 min, at 2˚C. Both plasma and haemolysates were used for biochemical analysis.

Statistical analysis:

All analysis were expressed as mean values ± SEM and analyzed by Student's t test. Differences were considered significant at $p < 0.05$ (Paulina and Aneta, 2019).

3. Results and Discussion

3.1. The total phenolic contents

The total phenolic contents in the extract of peach kernel, were as the following :(49 mg/g tannic acid equivalent) followed by flavonols (8.7 mg/g catechin equivalent), proanthocyandins (5.3 mg/g quercetin equivalent) and flavonoid (4.7 mg/g quercetin equivalent) as indicator to the plant extract possessed high phenol contents. The results agreement with (Mokrani ,2016) whereas reported to, on the basis of TPC and antioxidant activity parameters, high content of TPC, DPPH-RSA and FRP of peach extracts were obtained with values of 363 GAE/100 g, 48% percentage of inhibition and 317 AAE/100 g, respectively.

3.2. Antioxidant activity by DPPH radical scavenging method in the prepared nutraceuticals:

Table 1 showed the results of free radical scavenger activity of ascorbic acid, BHT, peach kernel extract nutraceuticals. In the present study different concentration ranged from 20 to 1000 µg/ml of ascorbic acid, BHT, peach kernel extracts nutraceuticals were evaluated against DPPH free radical. Ascorbic acid as standard showed the highest inhibition activity compared to BHT and both dietary against DPPH free radical. The results revealed that peach kernel extracts is very effective treatment against free radical. Also the activity increased with the increment of concentration till be stable at concentration 250 to 1000 µg/ml. The present results are in agreement with the results of (Rajendran, *et al*., 2010) who found that the scavenging effect of ascorbic acid increased with its concentration. The antioxidant scavenging activity of grape seeds was observed previously (Paulina and Aneta, 2019). In addition, DPPH scavenging method is easy and rapid in accordance with long stability of the free radical DPPH for evaluation of antioxidant activity (Mensor *et al*., 2001).

Table 1: Free radical scavenger activity of ascorbic acid, BHT, and peach kernel extract nutraceuticals.

Concentration (µg/ml)	Ascorbic acid	BHT	Peach kernel extract
20	73.8±0.300	1.34±0.237	7.1±0.345
30	78.8±0.278	17.7±0.149	28.8±0.213
40	81.9±0.193	50.2±0.750	53.2±0.335
50	83.8±0.111	57.1±0.225	73.3±0.333
100	87.1±0.301	72.1±0.223	77.4±0.373
250	98.7±0.130	89.1±0.051	93.8±0.251
500	98.8±0.130	88.8±0.331	93.8±0.251
750	98.9±0.135	88.8±0.211	93.9±0.252
1000	98.9±0.135	90.8±0.410	93.9±0.252

Briefly, the total concentration of phenolic compounds, was estimated to be around 3.4-4.5 mg/g kernel.)

3.3. Antioxidative activity of peach kernels extract by ABTS and ORAC assays:

The antioxidative activity of the analyzed peach kernels was evaluated using two different assays: radical scavenging capacity assay by ABTS and oxygen radical absorbance capacity (ORAC) (Table 2). The antioxidative activity of the peach kernels evaluated with the ABTS reach to25.80 ± 0.48a, and that analyzed by the ORAC method reach to 68.6 ± 3.02a.

On the other hand, the antioxidant activity of kernels was estimated with both DPPH and ABTS methods. In both assays, the samples showed strong ability to inhibit both free radicals tested. The estimation of the amount of the antioxidant activity was performed by the calibration curve of trolox for both DPPH and ABTS methods (Eq. 4 and Eq. 5, respectively)

$$\text{Abs (517 nm)} = -17.18 \times C_{\text{sample}} + 1.01 \quad (4)$$

As shown, after 24 h, 65-82% of the free radicals were inhibited, which indicate a strong antioxidant ability of the tested samples.

$$\text{Abs (734 nm)} = -0.001 \times C_{\text{sample}} + 0.947 \quad (5)$$

Also, the results from the ABTS assay, showed that after 40 min, 94% of the free radicals were scavenged. It was observed that not only the total content of polyphenols, but also the type of phenolic

compounds played a very important role in the antioxidative activity of peach kernels. The obtained results suggest that the antioxidative activity of peach kernels is the most related to the presence of total flavonols and flavons according to data as showed in (Table 2). About bioactive compounds identified by LC-MS in kernels separated from peach fruit (Paulina and Aneta, 2019) then to hydroxycinnamic acid (PC = 0.636 and 0.619 for ABTS and ORAC, respectively), and can also be ascribed to polymeric procyanidins (PC = 0.491 and 0.409 for ABTS and ORAC, respectively).

Moreover, (Mokrani, 2016) demonstrated that polyphenols present in all peach fruit extracts were potent anti-oxidative agents and suggested that cultivar might have a significant influence on the anti-oxidative activity of peach fruits. Although cyanogenic glucosides are claimed to be toxic with large amounts, it is assumed that in lower doses they may have pro-health properties. They have been found to exhibit high antimicrobial, antioxidant, anti-inflammatory and analgesic activities, and also to inhibit the development of human breast, intestine and liver cancer cells which was confirmed by in vitro analyses (Bak, 2010).

Briefly, Phenolic compounds, especially flavonoids and phenols have been shown to possess significant antioxidant activity.

Table 2: Enzyme of α-amylase. α-glycosidase, pancreatic lipase activities of analyzed peach kernel.

Parameters / Compound	Enzyme inhibition IC_{50} (mg of dried seeds)		
	α-Amylase	**α-Glucosidase**	**Pancreatic lipase**
Peach kernel extract (polyphenols)	3.70± 0.09k	2.60 ± 0.00f	0.47 ± 0.20m

Value ± SD are means of three repetitions, Mean values followed by different letters are statistically different at $p \leq 0.05$

3.4. Inhibitory activities of peach kernels toward digestive enzymes:

The inhibition capacity of the peach kernels extracts was evaluated towards α-glucosidase, α-amylase, and lipase as digestive enzymes. All of the peach kernel extracts as were tested for their inhibitory effect at different concentrations, which enabled calculating the IC_{50} values that are presented in (Table 3). Pancreatic lipase is a key enzyme in dietary fat absorption, responsible for the hydrolysis of 50-70% of dietary triglycerides into 2-monoacylglycerides and free fatty acids, which can then be absorbed by enterocytes. Inhibition of this enzyme is used to reduce dietary fat absorption and, therefore, the use of phytoextracts as pancreatic lipase inhibitors may represent an alternative approach for weight loss treatment (Sergent *et al.,* 2012). A positive correlation (PC) was observed between the inhibitory activity toward porcine pancreatic lipase and the total content of polyphenols (PC = 0.667). It is well known that polyphenols can bind proteins through hydrogen bonding or hydrophobic effects, leading to their aggregation and precipitation. However, the mechanism by which these substances inhibit pancreatic lipase is due to the synergy between many compounds of plant extracts (Birari and Bhutani, 2007).

Table 3: Antioxidant capacity of analyzed peach kernel by ORAC ABTS assays

Parameters / Compound	Antioxidant activity (mmol trolox/100 g dm	
	ORAC assay	**ABTS assay**
Peach kernel extract (polyphenols)	68.6 ± 3.02a	25.80 ± 0.48a

Value ± SD are means of three repetitions, Mean values followed by different letters are statistically different at $p \leq 0.05$

On the other hand, the results showed that type of phenolic compounds played an important role in the inhibitory capacity of peach kernels extract. The inhibitory activity of the peach kernels was the most related to the presence of total polymeric procyanidins (PC = 0.621), and hydroxycinnamic acid (PC = 0.509), but authors showed also that the oligomeric proanthocyanidins (contained in apples or seed grapes) were effective lipase inhibitors in vitro and prevent triglyceride absorption in human and in mice models (Sugiyama, 2007).

The incidence of obesity is associated with the incidence of diabetes type 2, characterized by elevated blood glucose levels. Type 2 diabetes represents 85 % of all diabetes cases and is the major cause of deaths among other diet-related diseases (Devalaraja, *et al.,* 2011). It was shown that

polyphenols have many biological activities and constitute an important part of the human diet also in the prevention of type 2 diabetes. Their hypoglycemic effect results from their antioxidative potential involved in restoring the insulin-secreting machinery in pancreatic cells, or abilities to inhibit the activity of carbohydrate-hydrolyzing enzymes (α-amylase and α-glucosidase) (Podsędek *et al*., 2014). Therefore, in this study the anti-α-amylase and -α-glucosidase activities were measured and the results are presented as IC_{50} values in Table 3.

The inhibitory effect toward α-amylase and α-glucosidase stimulated the most the content of polyphenols (PC = 0.524 and 0.727, respectively), but a highly positive correlation was also observed with contents of polymeric procyanidins (PC = 0.468 and 0.670, respectively), hydroxycinnamic acid (PC = 0.524 and 0.529, respectively).

Other researches (Boath, *et al*., 2012) suggested also that procyanidins are effective inhibitors of α-amylase activity as they form enzyme-tannin complexes, which prevents the enzyme from interacting with starch. In addition, these authors showed that flavonols can interact with hydroxy-cinnamic acids increasing the inhibition of α-glucosidase (Boath, *et al*., 2012).

Despite the promising results obtained in our study of inhibit lipase, α-amylase ,α-glucosidas and inhibition capacity , we carried out to confirm that plant components have the same effect in vivo an experimental model (male Albino rats), to evaluate effect it on prevent fat intake and carbohydrates absorption and that they do so at levels achievable from normal diets.

3.5. Plasma glucose levels:

In this study, the data as shown in table (4) recorded that, fasting plasma glucose levels were increased in diabetic control rats. When treated with peach kernel extract diabetic rats displayed significantly ($p<0.005$) decreased plasma glucose levels, close to the normal levels (Table 4).

3.5.1. Acute Toxicity of peach kernel extracts:

The peach kernel extract did not exhibit any observable signs of acute oral toxicity in experimental mice at the tested doses (200 mg/Kg BW, and 400 mg/Kg BW, respectively), throughout the 12-day experiment period. In addition, the behavioral and wellness parameters, such as the appearance of skin fur, salivation, mucous membrane, lethargy, eyes, convulsions, diarrhea, coma, tremors, sleep, and body weight were normal throughout the experimental period, and no mortality was recorded. Therefore, the LC_{50} of the extract was considered to be >400 mg/Kg BW according to the OECD guidelines (OECD, 2008). However, no significant weight change was witnessed in all groups ($p \geq 0.21$) treated with an increasing dose of peach kernel extract when compared with the vehicle control group (Table 4). All animals remained healthy till the last day of the experiment when compared with the control group. With taken consider to one human year almost equals two rat weeks (13.8 rat days) while correlating their entire life span , whereas ,laboratory rats live about 2-3.5 years (average 3 years), while the worldwide life expectancy of humans is 80 years, with variations in countries in accordance with their socioeconomic conditions, according the following equation:
(Therefore, taking their life span together), it can be calculated as:

$(80 \times 365) \div (3 \times 365) = 26.7$ human days = 1 rat day; and $365 \div 26.7 = 13.8$ rat days = 1 human year.

Subsequently, assay period (12 days) of acute Toxicity of peach kernel extracts assay on male albino rats is equal one year of human life span (Quinn , 2005 and Sengupta , 2012).

Table 4: Effect of peach kernel extract on body weight of rats.

Groups	1st Day	12th Day
	Body Weight (g)	
Group 1, control group	145 ± 5.6	155=/- 6.5
Group 2, (200 mg/kg PKE extract)	144 ± 4.6	156+/- 4.6
Group 3, (400 mg/kg PKE extract)	146 ± 5.4	159+/- 5.7

3.5.2. Effect of peach seeds extract on TBARS and CP:

The concentration of carbonylated proteins (CP) and TBARS in the plasma and liver of normal and diabetic rats is described in Table 5. In diabetic rats, TBARS and CP were significantly increased

in the plasma and liver tissue ($p<0.05$). Treatment of diabetic rats with beach kernel extract significantly decreased the concentration of both CP and TBARS in the plasma and liver tissue ($p<0.005$).

An imbalance between production and inactivation of ROS can lead to oxidative stress and damage to various biological macromolecules, and proteins exposed to ROS can suffer oxidative modifications that can lead to changes in their functions, and, consequently, affect cellular metabolism (Gupta and Ballal, 2015). In this context, measurement of protein carbonyl groups in biological samples is a reliable parameter with which to assess. ROS-mediated protein oxidation (Levine *et al*., 1990).

In this study, Treatment with peach kernel extract for 25 days (150 mg/kg body weight in a dose / day) showed a protein carbonyl content similar to the negative control, demonstrating no evidence of oxidative damage, and suggesting that these samples prevented H_2O_2-induced protein carbonylation. In the other hand, ROS can target lipids and initiate the lipid peroxidation process, which may lead to molecular cell damage (Gupta and Ballal, 2015). Also, the data showed no differences compared to the negative control at all concentrations tested in the H_2O_2 induced lipid peroxidation assay, which indicates the absence of lipid oxidative damage and hence the potential antioxidant action of peach kernel extract , consistent with the results of the ORAC and ABTS assay. These results are an important indication of the safety of treatment with peach kernel extract, because the occurrence of lipid peroxidation is directly related to various disease processes such as carcinogenesis and atherosclerosis.

Table 5: Effect of peach kernel extract on plasma glucose levels, the levels of lipid peroxides, carbonylated proteins and antioxidant enzyme activities in plasma and hepatic tissues in normal and diabetic rats.

	Normal control rats	**Diabetic control rats**	**Diabetic rats treated with peach seed extract**
		< 0.05.	< 0.05.
Plasma glucose (mg/dL)	4.80±0.24	15.19±0.59	5.00±0.24
Plasma TBARS (nmol/mL)	2.02±0.50	2.85±0.25*	2.07±0.48*
Plasma CP (nmol/ mg protein)	0.62±0.06	2.51±0.52	0.95±0.10*
RBC SOD (U/mg Hb)	3.18±0.15	1.60±0.15*	3.02±0.08*
RBC CAT(µmol H2O2utilized/min/mg	2.80±0.08	1.72±0.14*	2.61±0.06*
Liver TBARS (nmol/g of tissue)	0.84±0.03	1.86±0.17*	0.92±0.08
Liver CP (nmol/mg prot)	1.015±0.70	3.52±0.67	2.22±1.07
LiverSOD(Units/mgprot)	10.70±0.80	5.70+0.42*	9.70±0.75
LiverCAT(Units/mgprot)	75.2±1.46	44.8±1.36*	65.8±3.11

Whereas TBARS= thiobarbituric acid reactive substances, CP= carbonylated proteins, RBC= red blood cell lysate, SOD= superoxide dismutase and CAT= Catalase; * = significant at $P<0.05$, compared to normal control rats; + = significant at $P<0.05$, compared to diabetic control rats.

3.6. Effect of peach kernel extract on enzymatic antioxidants:

In diabetic rats, the activities of (Catalase) CAT and superoxide dismutase (SOD) were significantly decreased in the plasma and liver (Table 5) ($p<0.034$). The diabetic rats treated with peach kernel extract exhibited a significant increase in the activities of CAT and SOD in the plasma and liver ($p<0.005$).

Table 5 showed the effect of plant extract on the activities of antioxidant enzymes in the liver of control and experimental rats. There was a marked decreased in the percentage inhibition of superoxide dismutase, catalase and the level of GSH when compared with normal control group. However, the percentage inhibition of SOD, CAT and the level of GSH were significantly increased followed the oral administration of plant extract at 150 mg/kg body weight in a dose dependent manner.

In vivo lipid peroxidation study revealed that rats treated with peach kernel extract showed a significant increase ($P < 0.05$) in thiobarbituric acid reactive substances (TBARS) when compared with normal control group. Treatment with peach kernel extract for 25 days was able to lower the rise in thiobarbituric acid reactive substances (TBARS) level dose dependently as shown in Table 5.

3.7. Effect of peach kernel extract on Fasting Plasma glucose (mg/dL) Fig. 2 (a); and Plasma TBARS (nmol/mL) , carbonylated proteins (Plasma CP) (nmol/ mg protein) Liver CP (nmol/mg prot) Fig. 2 (b) ; and RBC SOD (U/mg Hb) , Liver SOD (Units/mg prot) , Liver CAT (Units/mg prot) Fig. 2 (c) ; and RBC CAT(µmol H_2O_2 utilized/min/mg Hb), Liver TBARS (nmol/g of tissue) Fig. 2 (d) of control group and diabetic rats groups.

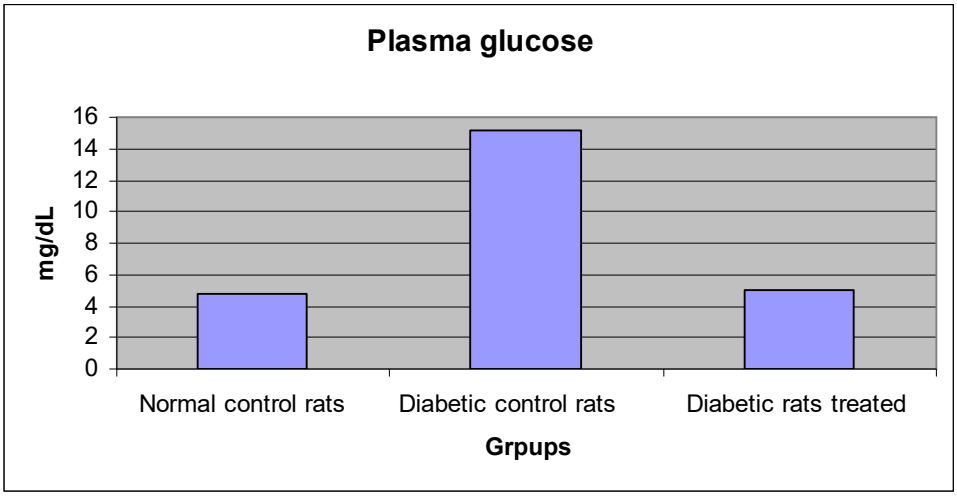

Fig. 2.a:

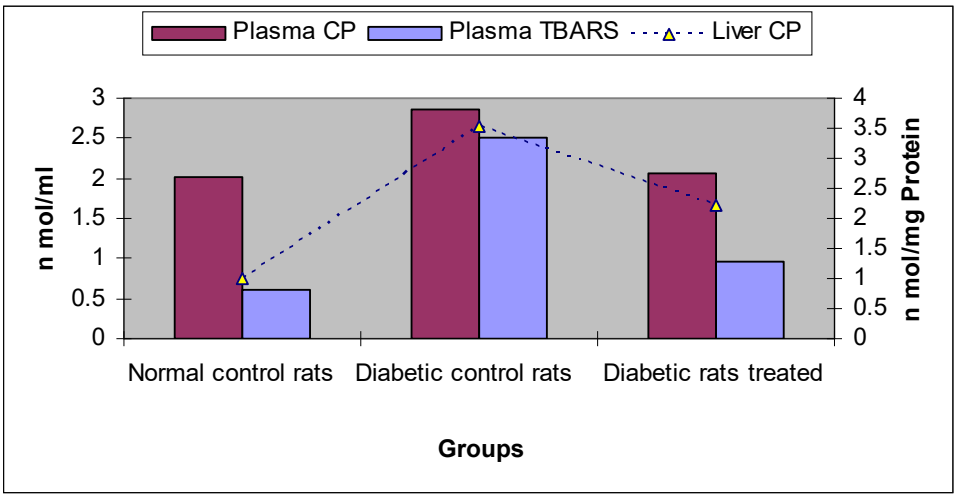

Fig. 2.b:

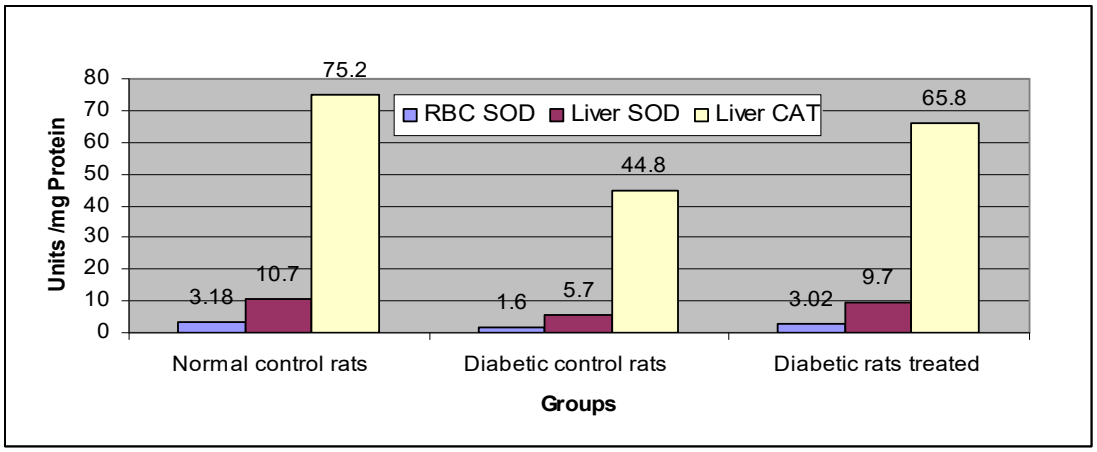

Fig. 2. C:

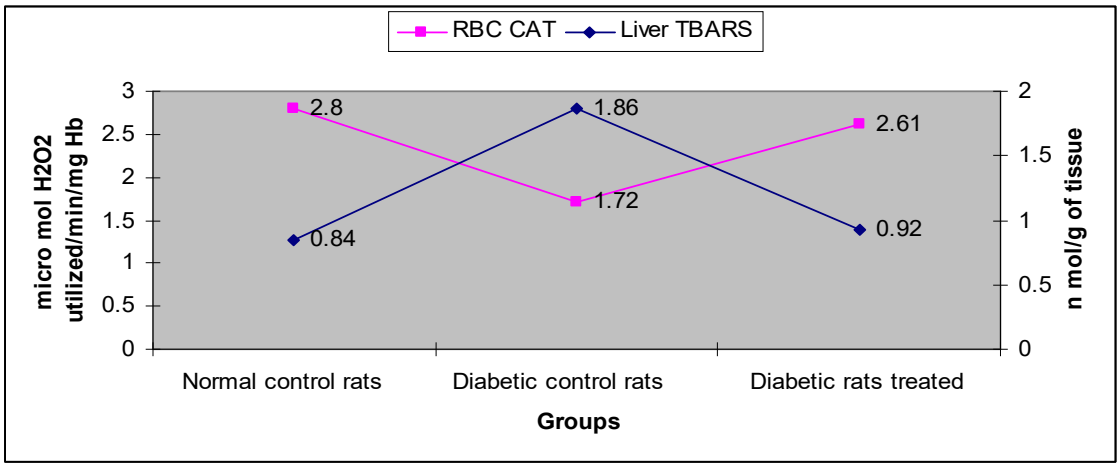

Fig. 2. d:

4. Discussion

Numerous studies report the antidiabetic effects of polyphenols as influenced on hyperglycemia through different unique mechanisms, including: inhibition of glucose absorption in the gut or of its uptake by peripheral tissues. The hypoglycemic effects of diacetylated anthocyanins at a 10 mg/kg diet dosage were observed with maltose as a glucose source (Matsui *et al*., 2002). This suggests that these effects are due to an inhibition of α-glucosidase in the gut mucosa. Inhibition of α-amylase and sucrase in rats by catechin at a dose of about 50 mg/kg diet or higher was also observed.

The inhibition of intestinal glycosidases and glucose transporter by polyphenols has been studied by Matsui *et al*. (2001). A recent study shows that quercetin has ability to protect the alterations in diabetic patients during oxidative stress. Ferulic acid (FA) is another polyphenol very abundant in vegetables and maize bran. Several lines of evidence have shown that FA acts as a potent anti-diabetic agent by acting at many levels. It was demonstrated that FA lowered blood glucose followed by a significantly increased plasma insulin and a negative correlation between blood glucose and plasma insulin (Barone *et al*., 2009).

On the other hand, Quercetin significantly protected the lipid peroxidation and inhibition antioxidant system in diabetics (Rizvi and Mishra, 2009).

Various proteins, including haemoglobin, albumin, collagen, LDL or crystalline proteins undergo non-enzymatic glycation (Klein, 1995). Glycation itself may induce the formation of oxygen-derived free radicals under diabetic condition (Gupta *et al.,* 1997). In the present study the administration of peach kernel (PK) extract decreased plasma glucose levels in diabetic rats and prevented STZ-induced oxidative stress. This suggests that treatment with the peach seed extract could mitigate the oxidative stress caused by hyperglycemia with STZ-induced in male albino rats. Lipid peroxidation is a characteristic of diabetes mellitus. Lipid peroxidation is a free-radical-induced process leading to oxidative deterioration of PUFA. Under physiological conditions, the concentrations of lipid peroxides in the tissues are low (Irina *et al.,* 2009) reported elevated levels of lipid peroxides in the plasma of diabetic rats. Lipid peroxide-mediated tissue damage resulted in the development of both type I and II diabetes.

A study performed by Lee *et al.* (2009) showed that polyphenols present in the extracts from *Hibiscus sabdariffa* attenuate diabetic nephropathy including pathology, serum lipid profile and oxidative markers in kidney.

Low levels of lipid peroxides stimulate the secretion of insulin, but when the concentration of endogenous peroxides increases, it may initiate uncontrolled lipid peroxidation, thus leading to cellular infiltration and islet cell damage in type I diabetes (Metz SA , 1984). The most commonly used indicators of lipid peroxidation are TBARS products (Lyons,1991). The increased lipid peroxidation in the tissues of diabetic animals may be due to the observed increase in the concentration of TBARS in the liver and kidney of diabetic rats (Stanely *et al.,* 2001). Our results in (Table 5) showed that in diabetic animals the levels of TBARS were high in the plasma and liver tissue, and were restored to normal values after the treatment with extract.

Carbonylation of proteins is a feature of irreversible oxidative damage, often leading to a loss of protein function, which is considered a wide spread indicator of severe oxidative damage and disease-derived protein dysfunction. Heavily carbonylated proteins tend to form high-molecular-weight aggregates which are resistant to degradation and accumulate as damaged or unfolded proteins. STZ-induced oxidative damage in proteins was revealed by the increased content of carbonylated proteins in the plasma and liver tissue (Cumaoglu *et al.,* 2007). The treatment of STZ-injected animals with peach seed extract lowered the proteins oxidant damage in rats plasma and liver tissues.

Oxidative stress in diabetes coexists with a reduction in the antioxidant capacity, which can increase the deleterious effects of the free radicals. Briviba *et al.* (2002) reported that SOD protects tissues against oxygen free radicals by catalyzing the removal of superoxide radical, converting it into H_2O_2 and molecular oxygen, which both damage the cell membrane and other biological structures (Arivazhagan *et al.,* 2000). Cheng *et al.,* (1981) carried out to catalase is a haem-protein, which is responsible for the detoxification of significant amounts of HO.

According to (Table 5) reduced activities of SOD and catalase in the liver and pancreas during diabetes were reported, resulting in a number of deleterious effects due to the accumulation of superoxide radicals and hydrogen peroxide (Saleem, *et al.,* 2017). In opposite the peach seed extract treated rats showed reduced lipid peroxidation and protein oxidation which was associated with an increased activity of SOD and CAT.

The antioxidant activity of phenols is due to their redox properties that allow them to act as reducing agents by donating hydrogen, quenching singlet oxygen or acting as metal chelators. Briefly, the antioxidant scavenging activity of peach kernel seeds was observed previously (Paulina and Aneta, 2019).

Therefore, we evaluated the acute oral toxicity effects of peach kernel extract of in experimental mice to appraise its safety. Research reports indicate that mice, just like humans, are sensitive to toxic compounds in plant extracts since their biological activities and genetics resemble those of humans to a greater degree (Saleem *et al.,* 2017).

We observed no mortality, abnormal behavior, or any acute oral toxicity associated signs in experimental animals that were administered with peach kernel extract, even at the limit dose of 400 mg/Kg BW. According to the OECD guidelines, a plant extract or chemical that do not elicit any observable signs of acute oral toxicity even at a dose of 400 mg/Kg BW is deemed safe. Therefore, the peach kernel extract was safe as its LD_{50} was greater than 400 mg/Kg BW; however, further toxicological investigations are necessary to exhaustively establish its safety and toxicity profile. Besides, research shows that orally administered chemical substances or drugs with $LD_{50} > 400$ mg/Kg BW are considered practically non-toxic and safe (Kifayatullah *et al.*, 2015). Elsewhere, similar results were obtained for single-oral dose (2000 mg/Kg BW) administration of C. fistula extracts in mice (Jothy *et al.,* 2011).

The same toward, amygdalin was determined using LC-MS analysis. In all samples the amount of amygdalin was ranged between 5.1-18 µg/g kernel (Karadimou C.C, 2017), this concentration is very low, which is an indication of no toxicity.

5. Conclusion

the results of the study provide a current understanding of the biological effects of polyphenols and their relationship to human health, including significant protection against the development of many chronic diseases, including cancer, diabetes, cardiovascular problems, and aging. Given this, peach extracts may be of great interest for application in food products and nutritional supplements. Because of this, it is interesting to test other peach seed extraction methods such as "green" technologies to increase the safety and quality of the products.

In addition, the mechanism of action of some of the effects of polyphenols is not fully understood; Such as the kinetics of absorption, accumulation, and elimination, will facilitate the design of such studies. The role of polyphenols in human health remains a fertile area of research. According to our current scientific understanding, polyphenols offer great hope for the prevention of chronic human diseases, especially diabetes mellitus and its side effects. This field is urgently needed.

In addition, this study provides important insights into the health properties and ameliorative effect of the kernel extract isolated from *Prunus persica* peach with respect to polyphenol compounds, antioxidant capacity, and ability in vitro to inhibit enzymes associated with hyperglycemia, obesity (α

- amylase, alpha-glucosidase, pancreatic lipase). Finally, we need to conduct further research in vivo (experimental animal) to confirm or rule out the health-promoting properties of peach kernel or kernel extract, Hence their potential as a source of bioactive compounds. In addition, the use of plant extracts requires toxicological and genotoxicological evaluations to establish and verify safety before adding them to food products. Moreover, the phenolic compounds in peach kernels can be a rich source of antioxidants for the production of fortified food products of natural origin such as fruit juices (energy drinks), purees, candies, soft drinks and so on.

Conclusion; Further studies are needed to apply this point to other animals, as well as investigate the molecular pathways involved in glucose homeostasis that may translate into long-term health benefits, which have not been observed in short-term studies.

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