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Phyto-Extracts of some by-Products/Wastes of Food Factories Attenuate Alloxan-Induced Diabetes Mellitus and its Complications in Rats

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Abstract:

The present study aims to investigate the effectiveness of three food processing by-products extracts including eggplant peel extract (EPP), onion skin extract (OSE), pomegranate peel extract (PPE) and their mixture in modulating the hyperglycemia using alloxane-induced diabetic rat model. Also, the effect of these extracts on diabetic complications including liver functions, serum lipid profile and antioxidant enzymes, the biomarkers of defense system in RBC's were also investigated. Treatment of rats with alloxan caused a significant ($p \leq 0.05$) increased in serum glucose level by the ratio 163.33% compared to normal control group. Phyto-extracts (EPE, OSE, PPE and their mixture, 150 mg/kg bw/day), lead to decrease this elevation value and recorded 71.17, 53.25, 57.17 and 47.30%, respectively, compared to normal control group. The maximum hypoglycemic yield was noticed for the extracts mixture treatment when compared with the rest of tested extracts individually. Also, phyto-extracts treatments attenuate the different diabetic complications including liver functions and serum lipid profile. The same treatment improve the antioxidant defense system in RBCs through elevation the activities of antioxidant enzymes (glutathione peroxidase, superoxide dismutase and catalase). In conclusion, the present study has demonstrated multiple beneficial effects of EPP, OSE and PPE in combating diabetes and diabetes-related complications. Thus, we recommended such phyto- extracts to be included in our daily diets, drinks, food supplementation and pharmacological formulae.

Keywords:,

Onion skin, eggplant peel, pomegranate peel, body weight, liver functions, blood glucose, serum lipid profile, antioxidant enzymes.

المستخلصات النباتية لبعض المنتجات الثانوية/النفايات لمصانع الأغذية تخفف من مرض السكري الذي يسببه الألوكسان ومضاعفاته في الفئران

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مستخلص البحث:

تهدف الدراسة الحالية إلى التحقق من فعالية ثلاثة مستخلصات نباتية من المنتجات الثانوية لمصانع الأغذية بما في ذلك مستخلص قشر الباذنجان (EPP) ومستخلص قشر البصل (OSE) ومستخلص قشر الرمان (PPE) ومزيجهم في تعديل ارتفاع السكر في الدم باستخدام الفئران المصابة بمرض السكري .كما تم فحص تأثير هذه المستخلصات على مضاعفات مرض السكري بما في ذلك وظائف الكبد ، ومستوى الدهون في الدم ، والإنزيمات المضادة للأكسدة ، والدلالات الحيوية لنظام الدفاع المضاد للاكسدة في كرات الدم الحمراء .تسبب معاملة الفئران بالألوكسان في زيادة معنوية ($p\leq 0.05$) في مستوى الجلوكوز في الدم بنسبة 163.33٪ مقارنة بالمجموعة الضابطة (الطبيعية) . أدت المستخلصات النباتية EPE، OSE، PPE وخليطها (150 ملجم / كجم من وزن الجسم / يوم) إلى خفض قيمة الارتفاع هذه حيث سجلت نسب 71.17 و 53.25 و 57.17 و 47.30٪ على التوالي مقارنة بالمجموعة الضابطة (الطبيعية) ..لوحظ ان الحد الأقصى من انخفاض مستوى سكر الدم قد سجل لمعاملة خليط المستخلصات بالمقارنة مع باقي المستخلصات المختبرة على حدة .أيضًا ، تخفف علاجات المستخلصات النباتية من مضاعفات مرض السكري المختلفة بما في ذلك وظائف الكبد وصورة الدهون في الدم .يحسن العلاج نفسه نظام الدفاع المضاد للأكسدة في كرات الدم الحمراء من خلال رفع مستوى أنشطة إنزيمات مضادات الأكسدة (الجلوتاثيون بيروكسيديز ، ديسموتاز الفائق والأكسدة الكاتلاز) . وفى النهاية،اظهرت الدراسة الحالية آثارًا مفيدة متعددة لـ EPP و OSE و PPEفي مكافحة مرض السكري والمضاعفات المرتبطة به .وبالتالي ، فقد أوصينا بإدراج هذه المستخلصات النباتية في وجباتنا الغذائية اليومية ، والمشروبات ، والمكملات الغذائية والتركيبات الدوائية .

الكلمات المفتاحية:

قشر البصل ، قشر الباذنجان ، قشر الرمان ، وزن الجسم ، وظائف الكبد ، جلوكوز الدم ، مستوى الدهون في الدم ، الإنزيمات المضادة للأكسدة.

1.Introducion

Diabetes mellitus is widely distributed all over the world including Egypt, and nearly one of each 10 person is diabetic. There is an estimated 143 million people worldwide suffering from diabetes, almost five times more than the estimates ten years ago. This number may probably double by the year 2030 (reviewed in Nagib, 2009). Diabetes is defined as a state in which homeostasis of carbohydrate and lipid metabolism is improperly regulated by insulin. This results primarily in elevated fasting and postprandial blood glucose levels. If this imbalanced homeostasis does not return to normalcy and continues for a protracted period of time, it leads to hyperglycemia that in due course turns into a syndrome called diabetes mellitus. Type 2 diabetes mellitus (T2DM) is one of the world's most common chronic diseases as changing lifestyles lead to reduced physical activity and increased obesity (Wild *et al.,* 2004). Early phenomenon of T2DM is insulin insensitivity, which not only has negative metabolic consequences (Panda and Kar, 2007 and Cunha *et al.*, 2008) but also contributes subsequent pancreas β-cell exhaustion, resulting in the onset of clinical hyperglycemia (Stumvoll *et al.,* 2005). Common T2DM health complications include heart, liver and kidney diseases, nerve damage, and other problems with feet, oral health, vision, hearing, and mental health (Lotfy et al., 2017; Elbasouny et al., 2019; Elhassaneen et al., 2020; Elhassaneen et al., 2022 a, b and e.) .

A number of ways to improve diabetic complications have been proposed, because early treatment and prevention play a pivotal role in reducing the population burden of diabetes. Benefits of pharmaceutical factors to treat the disease aggressively early have been recommended, but medications may have unwanted side effects. Thus, there has been a growing interest in herbal remedies that can be but have been difficult to maintain over a long term introduced into the general population with the least side effects and the maximal preventive outcome (Matsui *et al.,* 2006). In this context, many phytochemicals naturally occurring in plant parts would be desirable options. Amongest all of these bioactive compounds phenolic constiuents is represent the central position. Such compounds has been reported to improve diabetic status by decreasing oxidative stress or by reducing the disturbance of hepatic gene expressions (Dias *et al.,* 2005; Elbasouny et al., 2019; Elhassaneen et al., 2020; Elhassaneen et al., 2022- b),

Extensively studied sources of such natural compounds are fruits and vegetables, seeds, cereals, berries, wine, tea, onion bulbs, olive oil and aromatic plants. Attempts are also made to identify and evaluate these bioactive compounds in agricultural/ food processing by-products rich in antioxidant phenols that have nutritional importance and/or the potential for applications in the promotion of health and prevention against damages/complecations caused by many diseases including

diabetes mellitus. The resent study restricted on three ethanolic extracts of onion skin, and eggplant and apple peels.

Onion (*Allium cepa* L., Family: *Alliaceae*) skins are a source of flavor components and fiber compounds and particularly rich in quercetin glycosides (Hertog *et al*., 1992 and Waldron, 2001). The major flavonoids of mature onion bulbs are quercetin 3,40-*O*-diglucoside and quercetin 40-O-monoglucoside, accounting for more than 85% of the total flavonoids (Price and Rhodes, 1997). Also, phenolic compounds from onions skin is determined and could contribute significantly to antioxidant defense (Elhassanee and Sanad, 2009; Aly et al., 2017; Elbasouny et al., 2019)

Eggplant (*Solanum melongena*, Family: *Solanaceae*), one of the most widespread vegetable consumed around the world. Eggplant is ranked as one of the top ten vegetables in terms of oxygen radical scavenging capacity due to the fruit's phenolic constituents (Cao *et al.*, 1996). Antioxidant capacity and phenolic acid content are highly positively correlated in eggplant (Elhassaneen et al., 2023-b). Moreover, antioxidant capacity is related to skin colour and fruit size. Small purple fruit showed higher phenolic and anthocyanin contents and higher antioxidant capacity than did other eggplant fruit types (long green, large purple, medium-sized purple) (Nisha *et al.*, 2009). Also, Elhassaneen *et al.*, (2016) explained the antioxidant activity of methanol extracts of eggplant peel and its role in protecting the liver disorders induced by benzo(a)pyrene. (Elhassaneen *et al.*, 2016).

Pomegranates (*Punica granatum* L., *Lythraceae*) peels have been used extensively in the folk medicine of many cultures (Longtin, 2003 and Yunfeng *et al.*, 2006). Many studies found that pomegranate peel had the highest antioxidant activity among the peel, pulp and seed fractions of 28 kinds of fruits commonly consumed in China, as determined by FRAP (ferric reducing antioxidant power) assay (Guo *et al.*, 2003). Also, Also, phenolic compounds from apple peel is determined and could contribute significantly to antioxidant defense (Elhassaneen et al., 2014; Hassan, 2015). Also, pomegranate peel extract could effectively protect (after oral administration) against CCl4 induced hepatotoxicity, in which ROS damage was intensively involved (Murthy *et al.*, 2002).

It seems, therefore, that such previous food-processing by-product may be a rich source of natural antioxidants and worthy of further study. In the present study we try to open new avenue for extending the using of plant by-products in the therapeutic nutrition through evaluating the effectiveness of three extracts of onion skin, eggplant and apple peels, and their mixture in modulating hyperglycemia using alloxane-induced diabetic rat model. The effect of these extracts on diabetic complications including liver functions, serum lipid profile and antioxidant enzymes, the biomarkers of defense system in RBC's were also investigated.

2. Materials and Methods

2.1. Materials

2.1.1. Plant parts

Pomegranate (*Punica granatum*) and eggplant (*Solanum melongena*) fruits were purchased from Minia local markets, Minia City, Egypt. Red onion (*Allium cepa* L.) skin (ROS) was obtained by special arrangements with some fresh onion merchants, met Khorab village, Sinbellaween Center, Dakhlia Governorate, Egypt.

2.1.2. Chemicals

All chemicals (except other mention), solvents and buffers were of analytical grade were purchased from El-Ghomhorya Company for Trading Drugs, Chemicals and Medical instruments, Cairo, Egypt.

2.1.3. Kits

Kit's assays for glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) were purchased from BIODIAGNOSTIC, Dokki, Giza, Egypt. GSH-Px, GSH-Rd and CAT were assayed by the kits provided by MyBioSource, Inc., San Diego, CA, USA. SOD was assayed by the kits purchased from Creative BioLab, NY, USA. Triglycerides (TG), total cholesterol (TC), and albumin were purchased from El-Nasr Pharmaceutical Chemicals Company, Cairo, Egypt. HDL and LDL/VLDL cholesterol assay provided by Cell Biolabs, Inc., San Diego, CA, USA.

2.1.4. Equipment's

Absorbance (Abs) and fluorescence (FL) for different assays were measured using Labo-med. Inc., spectrophotometer, CA and Schematzu fluorescence apparatus, Japan, respectively.

2.2. Methods

2.2.1. Preparation of plant parts extracts

Plant parts extracts were prepared according to the methods of Aly et al., **(**2017) as follow: Eggplant and apple and red onion fruits were peeled manually to obtain eggplant and pomegranate peels, red onion skin. Skin and peels were washed then dried in a hot air oven (Horizontal Forced Air Drier, Proctor and Schwartz Inc., Philadelphia, PA) at 55 ^{0}C until arriving by the moisture in the final product to about 7%. The dried peels and skin were ground into a fine powder in high mixer speed (Moulinex Egypt, ElAraby Co., Egypt). The material that passed through an 80 mesh sieve was retained for use. Powders obtained were used for different types extracts as follow: A 20 g from dried plant powder plus 180 ml methanol (80%, v/v) were homogenized and transferred to a beaker and stirred at 200 rpm in an orbital shaker

(Unimax 1010, Heidolph Instruments GmbH & Co. KG, Germany) for 60 min at room temperature (25±5 ^{0}C). The extract was then separated from the residue by filtration through filter pPPEr (Whatman No. 1). The remaining residue was re-extracted twice, and then the two extracts were combined. The residual solvent of was removed under reduced pressure at 45°C using a rotary evaporator (Laborata 4000; Heidolph Instruments GmbH & Co. KG, Germany) and the extract could be ready for the basil diet blending purpose.

2.2.2. Biological Experiments

2.2.2.1. Ethical approval

The biological experiments of the present study were approved by the Scientific Research Ethics Committee (Animal Care and Use), Faculty of Home Economics, Menoufia University, Shebin El-Kom, Egypt (Approval no. 19- SREC-02-2020).

2.2.2.2. **Animals**

Normal male albino rats (140±3g) were obtained from Research Institute of Ophthalmology, Medical Analysis Department, Giza, Egypt.

2.2.2.3. **Basal diet (Standard diet)**

The basal diet (BD) was prepared according to Reeves *et al.*, (1993) as illustrated in table (A). The compositions of salt and vitamin mixtures are shown in tables (B and C).

2.2.2.4. **Induction of diabetic mellitus**

Diabetes was induced in normal healthy rats (30 rats) by subcutaneous injection with freshly prepared alloxan monohydrate in saline at a dose level of 150 mg/ kg body weight (Lazarow and Palay, 1954). Immediately after injection animals were received 5% glucose solution over night to overcome drug induced hypoglycemia (Wohaieb and Godin, 1987and Kakkar *et al.*,1998). After one week fast blood glucose (FBG) was analyzed using a specific by a drop of blood was obtained from tail vein and subjected to a strip of haemogluco test. All rats with FBG >200 mg/dl were considered to be diabetics and included in the study.

2.2.2.5. Experimental design

Biological experiments were achieved in accordance with the National Research Council's Institute of Laboratory Animal Resources, Commission on Life Sciences Rules (NRC, 1996). Rats (n=36) were housed individually in wire cages in a room maintained at 24 ± 2.0 ^{0}C and kept under normal healthy conditions. All rats were fed a basal diet (BD) for two week before beginning the experiment for

acclimatization. Total of 36 rats were divided in two main groups. Main group (1), six rats, served as normal controls were administered with saline intrapritoneally (IP), which was used as a vehicle for the treatment of animals, in alloxan (diabetic) group and fed basal diet (BD). Main Group (2), 30 rats were given alloxan to induce diabetes and divided into equal five subgroups as follow: group (2), fed on BD and served as positive control, and groups (3-6) fed on BD and administered by oral gavages, using a feeding needle with 150 mg/kg bw/day of EPE, OSE, PPE and ME (mixture, EPE, PPE and PPE by equal parts), respectively. Extracts concentration were selected for present experiments based on many of the results of previous studies (Hassan, 2015; Aly et al., 2017; and Elhassaneen et al., 2022-b). All the rats had free access to the diet and water as well as the treatments continued for a total duration of 4 weeks.

2.2.2.6. Biological evaluation

The diet consumed was recorded every day and body weight was recorded every week during the experimental period (28 days). The body weight gain (BWG, %), food intake (FI) and food efficiency ratio (FER) were determined according to Chapman *et al*., (1959) using the following equations: BWG (%)= (Final weight – Initial weight)/ Initial weight×100, FER= Grams gain in body weight (g/28 day)/ Grams feed intake (g/28 day).

2.2.2.7. Blood sampling

At the end of the experiment, after 12 hours of fasting, rats were anesthetized under the influence of ether and blood samples were collected using the abdominal aorta. Blood samples were taken in a dry clean glass centrifuge tubes and left to clot in water bath (37°C) for 28 minutes, then centrifuged for 10 minutes at 3000 rpm to separate the serum, which were carefully aspirated and transferred into clean cuvette tube and stored frozen at -20°C till analysis according to the method described by Schermer (1967). The erythrocyte residue was washed with three consecutive portions of sodium chloride solution (0.9%) and the blood was lysed with deionized water for 30 min. Haemolysate was then centrifuged at 30,000 rpm for 30 minutes. The supernatant fractions were transferred to a clean test tube and analyzed for antioxidant enzymes (Stroev and Makarova, 1989).

2.2.2.8. Hematological Analysis

Serum glucose

Serum glucose was determined by the colorimetric method explained by Tietz, (1976).

Liver functions

Aanine aminotransferase (ALT) and serum aspartate aminotransferase (AST) activities were measured in serum using the modified kinetic method of Tietz, (1976) while alkaline Phosphatase (ALP) activity was determined using modified kinetic method of Vassault *et al.,* (1999).

Serum lipid profile

Triglycerides (TGs), total cholesterol (TC), HDL-Cholesterol, and LDL-cholesterol and VLDL-cholesterol were determined in serum according to the methods of Fossati and PrenPPE (1982), Lopes-Virella et al., (1977) and Ahmadi et al., 2008, respectively.

Antioxidant enzymes

GSH-Px and CAT activities were determined as described by Splittgerber and Tappel, (1979) and Aebi, (1974), respectively. Superoxide dismutase (SOD) activity was measured by colorimetric assay according to the method of Mett and Müller (2021). Activities of SOD and GSH-Px enzymes were expressed in international unit per milliliter erythrocyte sediment and one unit of SOD was expressed as the enzyme protein amount causing 50% inhibition in 2- (4-iodophenyl)-3 (4-nitrophenol) 5-phenyltetrazolium chloride ($INTH_2$) reduction rate. GSH-Rd activity was determined according to the method recommended by the International Committee for Standardization in Haematology (ICSH, 1979).

2.3. Statistical Analysis

All measurements were carried out put in triplicates and expressed as mean± standard deviation (SD). Statistical analysis was performed with the Student *t*-test and MINITAB-12 computer program (Minitab Inc., State College, PA).

3. Results and Discussion

3.1. Effect of Phyto-extracts intervention on body weight gain, feed intake and feed efficiency ratio of diabetic rats

Table (1) show the effect of Phyto-extracts intervention on body weight gain, feed intake and feed efficiency ratio of diabetic rats. Such data indicated that the alloxane-treated rats exhibited significantly ($p \leq 0.05$) decreased in daily weight gain, daily feed intake and feed efficiency ratio compared to the normal group. All Phyto-extracts except OSE and the extracts mixture, 150 mg/kg bw/day, lead to decrease in all of these parameters compared to normal control group. The maximum negative effect was noticed for the extracts mixture treatment when compared with the rest of tested phyto-extracts individually.

Such data are in agreement with that observed by other plant parts extracts (Hasani- Ranjbar *et al*., 2010; Ajuru *et al*., 2019. Also, Hamzawy *et al.,* (2013)

reported that liver rat's disorders propably induced by diabetes reveal significant reduction of the body weight and feed intake. Furthermore, many studies noticed that DM and liver diseases could lead to malnutrition and the major causes of malnutrition in patients with DM and liver disease are poor dietary/feed intake, maldigestion, malabsorption and abnormalities in the metabolism and storage of nutrients (Elhassaneen *et al.,* 2014; Younis, 2016; Sayed Ahmed *et al.,* 2016; Aly *et al.,* 2017). Th the same context, several other studies reported that the decreasing in body weight gain and feed efficiency ratio in experimental animals were improved by consumption plant parts contains bioactive compounds such as found in the selected phyto- extracts (Elbanna, 2014; Mansour, 2017; Tahoon, 2019; Elhassaneen *et al.,* 2021).

Table 1. Effect of Phyto-extracts intervention on body weight gain, feed intake and feed efficiency ratio of diabetic rats

Group	Initial body weight (g)	Final body weight (g)	Daily weight gain (g)	Daily feed intake (g)	Feed efficiency ratio
Control (-) Std diet	140.35	289.51 ^{a}	6.55 ^{a}	14.77 ^{a}	0.443 ^{b}
Control (+) Diabetic	140.76	267.15^{b}	6.15 ^{a}	14.01 ^{ab}	0.439 ^{b}
EPE	140.39	258.12 ^{c}	5.98 ^{b}	13.61 ^{b}	0.439 ^{b}
OSE	141.15	271.50 ^{ab}	6.22 ^{a}	14.09 ^{a}	0.441 ^{b}
PPE	141.77	262.91 ^{bc}	6.08 ^{ab}	13.83 ^{b}	0.440 ^{b}
ME	141.07	214.04 ^{d}	5.19 ^{c}	9.83 ^{c}	0.528 ^{a}

* EPE, eggplant peel extract; OSE, onion skin extract; PPE, pomegranate peel extract and ME, mixture extract of EPE, OSE and PPE by equal parts. Each vale represent the mean value of six rats. Means in the same row with different superscript letters are significantly different at $p \leq 0.05$.

3.2. Effect of Phyto-extracts intervention on serum glucose concentration of alloxan-induced-diabetic rats

Effect of Phyto-extracts intervention on serum glucose concentration of alloxan–induced-diabetic rats was shown in Table (2). From such data it could be noticed that treatment of rats with alloxan caused a significant ($p \leq 0.05$) increased in serum glucose level by the ratio 163.33% compared to normal control group. Phyto-extracts (EPE, OSE, PPE and their mixture, 150 mg/kg bw/day), lead to decrease this elevation value and recorded 71.17, 53.25, 57.17 and 47.30%, respectively, compared to normal control group. The maximum hypoglycemic yield was noticed for the extracts mixture treatment when compared with the rest of tested extracts individually.

Such data are according with that obtained by several studies were conducted on powders or extracts of different plant parts of vegetables, fruits, algae, herbs,

medicinal and aromatic plants, etc. (Elbasouny et al., 2019; Elhassaneen et al., 2020; Elhassaneen et al., 2022 (b and e). Onion contains organosulfur compounds, *S*-methylcysteine sulfoxide (SMCS) and *S*-allylcysteine sulfoxide (SACS) which were linked to significant amelioration of hyperglycemia in diabetic rats (Sheela *et al.*, 1995). Similarly, Aly et al., 2017 found that a 0.5% extracts of onion skin,eggplant peel and tomato pomace also reduced hyperglycemia in streptozotocin-induced diabetic rats. This is could be due to the effects of bioactive compounds in such extract including quercetin on human diabetic lymphocytes showed a significant increase in the protection against DNA damage from hydrogen peroxide at the tissue level. Also, the phyto-extracts tested in the present study could be effect through improve glucose response and insulin resistance associated with diabetes by alleviating metabolic dysregulation of free fatty acids, suppressing oxidative stress, up-regulating glucose uptake at peripheral tissues, and/or down-regulating inflammatory gene expression in liver (Jung *et al.*, 2011, Hassan, 2015, Elhassaneen et al., 2021 b and c; Elhassaneen et al., 2022-b. They also reported that such activity may be related to diverse bioactive compounds present in EPE, OSE and PPE including phenolics,caroreoids, anthocyanins, lycopene and vitamins. Anthocyanins provide a myriad of health benefits including lower blood glucose level, management or control of postprandial hyperglycemia and reduce oxidative stress caused by diabetes (Hassan, 2015; Esther *et al.*, 2013 and Sepideh *et al.*, 2016). Finally, data of the present study proved that a combination of different extracts may be more efficient for reducing the serum glucose level compared with the individual one. Such phenomena could be due to the interactive effects occurred by their different categories of bioactive compounds which they contain. Such behavior was recorded in several previous studies (Sayed Ahmed, 2016; Aly et al., 2017; Elhassaneen *et al.*, 2016-a, 2021 a and b).

Table 2. Effect of Phyto-extracts intervention on serum glucose concentration (mg/dL) of alloxan–induced-diabetic rats*

Value	Control (-) Std diet	Control (+) Diabetic	Phyto-extracts intervention (150 mg/kg bw/day)			
			EPE	OSE	**PPE**	Mix
Mean	93.46 ^{d}	246.11^{a}	159.98 ^{b}	143.23 ^{c}	146.89 ^{bc}	137.67 ^{d}
SD	8.00	16.67	13.69	9.65	12.57	9.54
% of Change	0.00	163.33	71.17	53.25	57.17	47.30

* EPE, eggplant peel extract; OSE, onion skin extract; PPE, apple peel extract and ME, mixture extract of EPE, OSE and PPE by equal parts. Means in the same row with different superscript letters are significantly different at $p \leq 0.05$.

3.3. Effect of Phyto-extracts intervention on liver functions enzymes activity of alloxan-induced-diabetic rats

Effect of Phyto-extracts intervention on liver functions enzymes activity of alloxan-induced-diabetic rats was shown in Table (3). From such data it could be

noticed that treatment of rats with alloxan caused a significant ($p \leq 0.05$) increased in liver functions enzymes activities i.e. ALT, AST and ALP, by the ratio of 65.91, 41.38 and 31.56% compared to normal control group. Phyto-extracts (EPE, OSE, PPE and their mixture, 150 mg/kg bw/day), lead to decrease this elevation value and recorded 43.03, 25.55, 35.96 and 12.48% (ALT), 29.78, 20.44, 23.04 and 14.11% (AST), and 23.41, 19.63, 21.51 and 16.52% (ALP), respectively, compared to normal control group. The maximum improved effect was noticed for the extracts mixture treatment when compared with the rest of tested extracts individually.

Aminotransferases (ALT and AST) are normally intracellular enzymes and the presence of elevated levels them in the plasma indicates damage to cells rich in these enzymes. Such present data are according with that obtained by several studies were conducted on powders or extracts of different plant parts of vegetables, fruits, algae, herbs, medicinal and aromatic plants, etc. (Hassan, 2015; Elbasouny et al., 2019; Elhassaneen et al., 2013; 2021 d and e; Elsemelawy et al., 2021). The effects of such extracts could be attributed to their high level content of bioactive compounds. Our present data with the others reported that OSE, EPE and TPE are a rich source of different classes of bioactive compounds such flavonols, phenolic acids, anthocyanins, alkaloids, carotenoids, phytosterols and organosulfur compounds (Rodriguez *et al*., 1994; Velioglu *et al*., 1998; Beattic *et al.*, 2005 Elhassaneen and Sanad, 2009; Elbasouny et al., 2019; Abd Elalal et al., 2021; Elhassaneen et al., 2016, Aly et al., 2017; Elhassaneen et al., 2022 a,b and c; Elhassaneen et al., 2023 a and b)**.**

The potential mechanism of action of liver serum enzymes-lowering activity of the tested extracts including EPE, OSE, PPE and their mixture, could be illustrated by one or more of the following : 1) phenolic compounds found in all the tested extracts are known to block the hepatocellular uptake of bile acids (ElSamouny, 2021; Elhassaneen et al., 2021 a, c and d), 2) phenolics constituents pretreatment improved the biological effects of the liver i.e. antioxidant and scavenging activities, and inhibition the lipid oxidation (Beattic *et al.*, 2005; Aly et al., 2017); and 3) carotenoids and anthocyanins reduce the damage of hepatocytes, inhibition the low density lipoprotein peroxidation, and scavenge the of reactive oxygen species (ROS) (Sayed Ahmed, 2016; Aly et al., 2017; Elhassaneen et al., 2022 a and b). On the other side, data of the present study proved that a combination of different extracts may be more efficient in improving of the serum liver function enzymes activities disorders induced by diabetes compared with the individual one. Such phenomena could be due to the interactive effects occurred by their different categories of bioactive compounds which they contain. Such behavior was recorded in several previous studies (Aly et al., 2017; Elbasouny et al., 2019; Elhassaneen *et al.*,2022-a).

Table 3. Effect of Phyto-extracts intervention on liver functions enzymes activity of alloxan-induced-diabetic rats *

Value	Control (-) Std diet	Control (+) Diabetic	Phyto-extracts intervention (150 mg/kg bw/day))			
			EPE	OPE	PPE	ME
Serum alanine aminotransferase (ALT) activity (U/L)						
Mean	30.88 ^{c}	51.24 ^{a}	44.17 ^{ab}	38.78 ^{b}	41.99 ^{b}	34.74 ^{bc}
SD	1.87	4.39	2.67	3.32	4.09	2.97
% of Change	0.00	65.91	43.03	25.55	35.96	12.48
Serum Aspartate aminotransferase (AST)activity (U/L)						
Mean	52.53 ^{c}	74.26 ^{a}	68.17 ^{a}	63.27 ^{b}	64.63 ^{ab}	59.94 ^{b}
SD	4.50	6.36	5.84	5.42	5.53	5.13
% of Change	0.00	41.38	29.78	20.44	23.04	14.11
Serum alkaline phosphatase (ALP,U/L)						
Mean	148.45 ^{c}	195.30 ^{a}	183.20 ^{a}	177.59 ^{b}	180.38 ^{ab}	172.97 ^{b}
SD	10.67	15.54	11.76	15.20	15.44	12.08
% of Change	0.00	31.56	23.41	19.63	21.51	16.52

* EPE, eggplant peel extract; OSE, onion skin extract; PPE, apple peel extract and ME, mixture extract of EPE, OSE and PPE by equal parts. Means in the same row with different superscript letters are significantly different at $p \leq 0.05$.

3.4. Effect of Phyto-extracts intervention on serum lipid profile levels of alloxan-induced diabetic rats

Effect of Phyto-extracts intervention on serum lipid profile of alloxan-induced-diabetic rats was shown in Table (4). From such data it could be noticed that treatment of rats with alloxan caused a significant ($p \leq 0.05$) decreased in serum lipid profile i.e. TG, TC, LDL-c and VLDL-c, by the ratio of 38.72, 35.32, 95.60 and 38.72%, compared to normal control group. Phyto-extracts (EPE, OSE, PPE and their mixture, 150 mg/kg bw/day), lead to decrease this elevation value and recorded 26.85, 21.28, 20.18 and 12.15% (TG), 24.95, 18.24, 19.97 and 14.92% (TC), 68.30, 49.45, 54.61and 37.55% (VLD-c), and 26.85, 21.28, 20.18 and 12.15% (VLDL-c), respectively, compared to normal control group. The opposite direction was recorded for the HDL-c. The maximum hyperlipidemic effect was noticed for the extracts mixture treatment when compared with the rest of tested extracts individually.

Coronary heart disease (CHD) represents one of the most complications induced by diabetes which represent a major health problem all over the world. Several studies have now reported that blood elevated concentrations of LDL-c and lowered of HDL-c in the blood are powerful risk factors for CHD (reviewed in Bedawy, 2008). The composition of the human diet plays an important role in the

management of lipid and lipoprotein levels in the blood. Recently, the possible hypocholesrerolemic effects of several dietary constituents , such as found in our selected extracts (EPE, OSE, PPE and theur mixture) including, phenolics, carotenoids, anthocyanins, alkaloids, lycopene, phytosterols and organosulfur compounds etc., have attracted much interest. Such present observations are according with that obtained by several studies were conducted on powders or extracts of different plant parts of vegetables, fruits, algae, herbs, medicinal and aromatic plants, etc. (Hassan, 2015; Elbasouny et al., 2019; Elhassaneen et al., 2020, 2021 a and b). The possible hypocholesrerolemic effects of several dietary constituents of the tested extracts including EPE, OSE, PPE and their mixture, could be illustrated by one or more of the following : 1) phenolics constituents pretreatment improved the biological effects of the liver i.e. antioxidant and scavenging activities, and inhibition the lipid oxidation (Beattic *et al.*, 2005; Aly et al., 2017); 2) carotenoids and anthocyanins inhibited the low density lipoprotein peroxidation, and scavenge the ROS, then protect the endothelial cell damage which is believed to be involved in the early development of atherosclerosis). (Kaneko *et al.*, 1994Sayed Ahmed, 2016; Aly et al., 2017; Elhassaneen et al., 2022 a and b), 3) phenolic compounds exerts its beneficial effects on cardiovascular health by antioxidant and anti-inflammatory activities *(*Kuhlmann *et al.*, 1998), and 4) phenolics and carotenoids reduced LDL oxidation *in vitro* from various oxidases including 15-lipoxygenase, copper-ion and linoleic acid hydroperoxide (Kaneko *et al.*, 1994 and Alaa *et al.*, 2015; Aly et al., 2017).

Table 4. Effect of Phyto-extracts intervention on serum lipid profile levels of alloxan-induced diabetic rats *

Value	Control (-) Std diet	Control (+) Diabetic	Phyto-extracts intervention (150 mg/kg bw/day))			
			EPE	OPE	PPE	ME
Triglycerides (TG, mg/dL)						
Mean	53.32 ^{c}	73.97 ^{a}	67.64 ^{a}	64.67 ^{b}	64.08 ^{ab}	59.80 ^{b}
SD	5.32	6.19	3.86	4.51	7.11	5.17
% of Change	0.00	38.72	26.85	21.28	20.18	12.15
Total cholesterol (TC, mg/dL)						
Mean	109.13 ^{d}	147.68 ^{a}	136.35 ^{b}	129.03 ^{b}	130.93 ^{b}	125.41 ^{b}
SD	7.62	7.99	9.52	6.08	9.14	10.65
% of Change	0.00	35.32	24.95	18.24	19.97	14.92
High density lipoprotein (HDL, mg/dL)						
Mean	45.62 ^{a}	29.52 ^{a}	33.89 ^{b}	37.12 ^{ab}	36.40 ^{b}	40.76 ^{a}

SD	4.08	1.89	2.37	2.76	2.54	1.88
% of Change	0.00	-35.30	-25.71	-18.64	-20.20	-10.65
Low density lipoprotein (LDL, mg/dL)						
Mean	52.85 [d]	103.37 [a]	88.94 [b]	78.98 [bc]	81.71 [b]	72.69 [c]
SD	3.90	7.21	5.90	5.51	6.03	6.06
% of Change	0.00	95.60	68.30	49.45	54.61	37.55
Very low density lipoprotein (VHDL, mg/dL)						
Mean	10.66 [b]	14.79 [a]	13.53 [a]	12.93 [a]	12.82 [a]	11.96 [a]
SD	0.79	2.01	0.94	1.76	0.89	1.02
% of Change	0.00	38.72	26.85	21.28	20.18	12.15

* EPE, eggplant peel extract; OSE, onion skin extract; PPE, apple peel extract and ME, mixture extract of EPE, OSE and PPE by equal parts. Means in the same row with different superscript letters are significantly different at $p \leq 0.05$.

3.5. Effect of phyto-extracts on erythrocytes antioxidant enzymes activities of alloxan-diabetic rats

The effect of phyto-extracts on antioxidant defense system in erythrocytes of alloxan-diabetic rats were shown in Table (5). From such data it could be noticed that diabetic mellitus induced a significant ($p \leq 0.05$) decreased in glutathione peroxidase (GSH-Px), glutathione reductase (GSH-Rd), catalase (CAT) and superoxide dismutase (SOD) activities in RBC's by -43.61, -35.47, -30.96 and -38.59% compared to normal controls, respectively. Phyto-extracts (EPE, OSE, PPE and their mixture), 150 mg/kg bw/day), lead to increase this diminishing and recorded -26.56, -18.27, -20.25 and -11.35% (GSH-Px); -28.30, -17.36, -23.40 and -13.96% (GSH-Rd); -17.65, -13.96, -15.83 and -8.26% (CAT); -23.02; -17.66, -19.09 and -14.97% (SOD), respectively, compared to normal control group. The maximum improved effect was noticed for the extracts mixture treatment when compared with the rest of tested extracts individually. Such data are in partially accordance with that reported by several authors (Elbasouny et al., 2019; Abd Elalal et al., 2021 and 2022; Elhassaneen et al., 2022 (a and d); Gharib et al., 2022).

Oxidative stress (OS) is a phenomenon caused by an imbalance between production and accumulation of free radicals (ROS, RNS etc.) in cells and tissues and the ability of a biological system such as RBC's to detoxify these reactive products (Pizzino et al., 2017). To prevent OS activities, the organism has developed antioxidant defenses largely based on antioxidant enzymes able to scavenge the free radicals. Antioxidant enzymes include SOD is responsible for the reduction of $O_2^{\cdot-}$ to H_2O_2 and multiple enzymes will remove H_2O_2 including GSH-Px and CAT. Also, the GSH reduces the selenium and the reduced form of the enzyme (GSH-Px) then

react with H_2O_2. Finally, GSH-Rd enzyme catalyze the reaction of GSSG back to GSH ($GSSG + NADPH + H^+ \rightarrow 2GSH + NADP^+$) (Thomas *et al*., 1990).

Several studies reported that antioxidant enzymes systems are active in liver cells (Galinier *et al.*, 2004; Cao, 2014). Diminishing the activity of the antioxidant enzyme results in increased ROS production and mitochondrial dysfunction (Elhassaneen, 1996; Curtis *et al.*, 2010). The phyto extracts and their mixtures tested in the current study are rich in bioactive compounds such phenolics, organosulphur compounds, carotenoids , lycopene, anthocyanins, quercetin etc., which exhibited biological activities including antioxidant and scavenging activities, and inhibition the lipid perioxidation (Elhassaneen and Sanad, 2009; Elhassaneen *et al.*, 2016-a; Mashal, 2016; Aly et al., 2017; Elbasouny et al., 2019; Abd Elalal et al., 2021; Elhassaneen et al., 2023 a and b). Such biological properties are important in doctrinaire of the diabetes mellitus development through free radicals scavenging processes in RBC's.

Table 5. Effect of phyto-extracts on erythrocytes antioxidant enzymes activities of alloxan-diabetic rats*

Value	Control (-) Std diet	Control (+) Diabetic	Phyto-extracts intervention (150 mg/kg bw/day))			
			EPE	OPE	PPE	ME
Glutathione peroxidase (GSH-Px, U/g Hb)						
Mean	19.65 ^{a}	11.08 ^{c}	14.43 ^{b}	16.06 ^{b}	15.67 ^{b}	17.42 ^{ab}
SD	2.03	1.32	1.01	1.34	2.03	1.22
% of Change	0.00	-43.61	-26.56	-18.27	-20.25	-11.35
Glutathione reductase (GSH-Rd, U/g Hb)						
Mean	2.65 ^{a}	1.71 ^{c}	1.90 ^{b}	2.19 ^{ab}	2.03 ^{b}	2.28 ^{a}
SD	0.09	0.21	0.15	0.15	0.14	0.10
% of Change	0.00	-35.47	-28.30	-17.36	-23.40	-13.96
Catalase (CAT, U/g Hb)						
Mean	176.24 ^{a}	121.67 ^{d}	145.13 ^{c}	151.64 ^{c}	148.34 ^{c}	161.67 ^{b}
SD	13.67	10.76	10.13	11.09	10.35	12.32
% of Change	0.00	-30.96	-17.65	-13.96	-15.83	-8.26
Superoxide dismutase (SOD, U/g Hb)						
Mean	4.68 ^{a}	2.88 ^{c}	3.60 ^{b}	3.86 ^{ab}	3.79 ^{b}	3.98 ^{a}
SD	0.22	0.20	0.19	0.27	0.29	0.30
% of Change	0.00	-38.59	-23.02	-17.66	-19.09	-14.97

* EPE, eggplant peel extract; OSE, onion skin extract; PPE, apple peel extract and ME, mixture extract of EPE, OSE and PPE by equal parts. Means in the same row with different superscript letters are significantly different at $p \leq 0.05$.

In conclusion, the current study has demonstrated the potency of phyto-extracts including EPE, OSE and PPE to attenuate the hyperglycemia in diabetic rats. Also,

phyto-extracts treatments ameliorate the different diabetic complications including liver functions and serum lipid profile. Furthermore, the same treatment improve the antioxidant defense system in RBCs through elevation the activities of antioxidant enzymes (glutathione peroxidase, superoxide dismutase and catalase). Thus, these findings provide a basis for the use of phyto-extracts (EPE, OSE and PPE) and also have important implications for the prevention and early treatment of T2DM.

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