Potential roles of some plant parts on oxidant/antioxidant status and hyperglycemia in diabetic rat

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مجلة البحوث في مجالات التربية النوعية

معرف البحث الرقمي DOI: 10.21608/jedu.2021.55631.1176

المجلد السادس . العدد التاسع والعشرين . يوليو 2020

الترقيم الدولي

P-ISSN: 1687-3424 E- ISSN: 2735-3346

موقع المجلة عبر بنك المعرفة المصري https://jedu.journals.ekb.eg/

موقع المجلة http://jrfse.minia.edu.eg/Hom

العنوان: كلية التربية النوعية . جامعة المنيا . جمهورية مصر العربية

الأدوار المحتملة لبعض أجزاء النبات في حالة الأكسدة / مضادات الأكسدة وارتفاع السكر في الدم في الفئران المصابة بداء السكري

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ينتشر مرض السكري على نطاق واسع في جميع أنحاء العالم بما في ذلك مصر. ويشمل ارتفاع سكر الدم ، اختلال حالة الأكسدة / مضادات الأكسدة ، أكسدة/ سمية الدهون/ السية والالتهابات منخفضة الدرجة كأسباب رئيسية لمضاعفات مرض السكري. لذلك تم اقتراح العديد من الاستراتيجيات لتحسين هذه المضاعفات حيث يلعب العلاج المبكر والوقاية من مضاعفات مرض السكري دورًا محوريًا في تقليل العبء السكاني لمرض السكري. لذلك تهدف الدراسة الحالية إلى التحقق من فعالية ثلاثة من مساحيق الأجزاء النباتية الأكثر شيوعًا (أوراق التوت وتفل الطماطم وقشر البطاطس) في تعديل ارتفاع السكر في الدم وحالة الأكسدة / مضادات الأكسدة باستخدام الفئران المصابة بداء السكري التي يسببها الألوكسان. تسبب علاج الحيوانات بالالوكسان في زيادة معنوية ($p\leq0.05$) في تركيز الجلوكوز في الدم بنسبة 113.48٪ مقارنة بالمجموعة الضابطة العادية. أدى إضافة 5٪ من أجزاء النبات المختارة إلى أعلاف الفئران وهى أوراق التوت ومسحوق تفل الطماطم ، ومسحوق قشر البطاطس ، ومزيجها إلى انخفاض هذه القيمة بمعدل −18.25 ، −23.20 ، −20.93 ، −26.80٪ على التوالي. تم تسجيل نفس السلوك لمستوى المالونالدهيد (MDA) في أنسجة الكبد ، وهي احدى المؤشرات الحيوية الهامة للإجهاد التأكسدي والتهاب الكبد. كذلك ، تم تحفيز تحسين وظائف الكبد ونظام الدفاع المضاد للأكسدة والتى تشمل مستوى الجلوتاثيون (GSH) في أنسجة الكبد ، والإنزيمات المضادة للأكسدة والفيتامينات في مصل الدم في الفئران المصابة بداء السكري بمعدلات مختلفة نتيجة لخلط وتدعيم النظام الغذائي بأجزاء النبات المدروسة. يمكن أن تُعزى كل هذه التأثيرات بشكل أساسي إلى الأنشطة المضادة للأكسدة القوية لهذه الأجزاء النباتية نتيجة لمحتواها العالي من المركبات النشطة بيولوجيًا. وفى النهاية، يمكن أن توفر هذه النتائج أساسًا علميا لاستخدام مساحيق الأجزاء النباتية المختارة للوقاية والعلاج المبكر لمرض السكري من النوع الثانى.

الكلمات المفتاحية: ورق التوت، تفل الطماطم ، قشر البطاطس، وظائف الكبد ، الإنزيمات المضادة للأكسدة.

Potential roles of some plant parts on oxidant/antioxidant status and hyperglycemia in diabetic rat

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Abstract: Diabetes mellitus (DM) is widely distributed all over the world including Egypt. Hyperglycemia, oxidant/antioxidant status defect, lipid oxidation/toxicity and low- grade inflammation as major causes on diabetic complications. Several strategies to improve these complications have been suggested. Early treatment and prevention of such diabetes complications play a pivotal role in reducing the population burden of diabetes. Therefore, the present study aims to investigate the effectiveness of three most commonly plant parts powder (mulberry leaves, tomato pomace and potato peel) in modulating hyperglycemia and oxidant/antioxidant status using alloxane-induced diabetic rats. Treatment of animals with alloxan caused a significant increased ($p \leq 0.05$) in serum glucose concentration by the ratio of 113.48% compared to normal controls. Supplementation of the rat diets with 5% of the selected plant parts including mulberry leaves (MLP), tomato pomace powder (TPP), potato peel powder (PPP) and their mixture (Mix) leads to decrease this value by the rate of -18.25, -23.20, -20.93 and -26.80%, respectively. The same behavior was recorded for liver tissue MDA level, the biomarkers of oxidative stress and inflammation in liver. Also, improving in liver functions and antioxidant defense system (GSH in liver tissue, and antioxidant enzymes and vitamins in serum) in diabetic rats have been induced by different rates as the result of supplementation the diet with the studied plant parts. All of these effects could be principally attributed to the strong antioxidant activities of these plant parts as the result of their high bioactive compounds content. These findings provide a basis for the use of the selected plant parts powder for the prevention and early treatment of type-2 diabetes.

Keywords: mulberry leaves, tomato pomace, potato peel, liver functions, antioxidant enzymes.

Introduction

Diabetes is defined as a metabolic disorder characterized by hyperglycemia and insufficiency of secretion or action of endogenous 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 , DM (WHO, 1999 and Tiwari and Madhusudana, 2002). There are two main categories of this disease. Type 1 diabetes mellitus (T1DM) also called insulin-dependent diabetes mellitus (IDDM) and Type 2 (T2DM), the noninsulin- dependent diabetes mellitus (NIDDM). IDDM represents a heterogeneous and polygenic disorder, with a number of non-human leukocyte antigen (HLA) loci (about 20) contributing to the disease susceptibility

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 but also contributes subsequent pancreas β-cell exhaustion, resulting in the onset of clinical hyperglycemia (Stumvoll, et al., 2005). Thus, understanding the regulation of the insulin response and identifying the related mechanisms are important to early treatment and prevention of T2DM. DM is widely distributed all over the world including Egypt, and nearly one of each 10 person is diabetic. According to World Health Organization (WHO) reports, the number of people with diabetes increased from 108 million in 1980 to 422 million in 2014 (www.who.int/ar/news-room/fact-sheets/detail/diabetes). The global prevalence of DM increased in adults over the age of 18 years from 4.7% in 1980 to 8.5% in 2014. The premature death rate from diabetes increased by 5% between 2000 and 2016. In 2016, diabetes was a direct cause of nearly 1.6 million deaths. And in 2012, high blood glucose caused another 2.2 million deaths. Almost half of all deaths attributed to high blood glucose occur before the age of 70 The prevalence of diabetes is higher in low and middle income countries than in high income countries (Tiwari and Madhusudana, 2002). DM is a major cause of

blindness, kidney failure, heart attacks, strokes, and lower limb amputations. (Konstantinos ,et al., 2018).

On the other side, iincreased oxidative stress (OS) is a widely accepted participant in the development and progression of DM and its complications (Baynes and Thorpe , 1999; Ceriello, 2006; and Ceriello , 2000).). Diabetes is usually accompanied by increased production of free radicals or impaired antioxidant defenses (Halliwell and Gutteridge ,1990). Excessively high levels of free radicals as the result of OS cause damage to cellular proteins, membrane lipids and nucleic acids, and eventually cell death. Various mechanisms have been suggested to contribute to the formation of these reactive oxygen-free radicals. So, extensive studies of pharmacological interventions based on biological antioxidants have been carried out (Matsui ,et al., 2006; Elhassaneen , et al., 2016; and Aly, et al., 2017). Biological antioxidant defense systems involve both enzymatic and nonenzymatic strategies. Common antioxidants include enzymes, e.g. superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), and glutathione reductase (GSH-Rd); vitamins, e.g. vitamins A, C, and E; biological macromolecules, i.e. glutathione; phytochemicals, i.e. bioflavonoids, phenolics, lipoic acid carotenoids and coenzyme Q10; minerals, i.e. copper, zinc, manganese, and selenium; and the cofactors, i.e.folic acid and vitamins B1, B2, B6, B12. All of these antioxidants are working in synergy with each other and against different types of free radicals (Sayed-Ahmed, 2016 and Aly ,et al., 2017).

Extensively studied sources of such natural antioxidants 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 by-products, ethnic and traditional products, herbal teas, cold pressed seed oils, exudates resins, hydrolysis products, not evaluate fruits and edible leaves and other raw materials rich in antioxidant phenols that have nutritional importance and/or the potential for applications in the promotion of health and prevention against damages/complications caused by many diseases including DM. Amongst of these agricultural by-

products, Tomato (Lycopersicon esculentum L.) pomace and Potato (Solanum tuberosum L.) peel are producing in large quantities in food-processing plants. Also, mulberry (Morus alba L.) leaves which produces in large quantities from the huge mulberry trees that grow wild along waterways, highways and agricultural roads, with little use.

Tomato juice is the most important vegetable juice with respect to per capita consumption. About 3–7% of the raw material is lost as waste during tomato juice pressing (Otto and Sulc, 2001). Tomato pomace consists of the dried and crushed skins and seeds of the fruit (Avelino, et al., 1997). Lycopene is the principal carotenoid causing the characteristic red hue of tomatoes. Most of the lycopene is associated with the water-insoluble fraction and the skin (Sharma and Maguer, 1996). Therefore, skin extracts are especially rich in lycopene. Baysal et al., (2000) clearly stated that a large quantity of carotenoids is lost as waste in tomato processing. Lycopene is associated with antioxidant status, gap-junction formation, inhibition of cholesterol synthesis and prevent cancer and heart diseases (Weisburger, 1998 and Betty, 2002; and Aly, et al., 2017). Potato is the largest vegetable crop worldwide, amounting to approximately 320 million metric tons annually (FAO, 2005). Processing of potatoes (mainly for the production of chips, French fries, and dehydrated products) has presented a steady increase during the last decades, exceeding considerably the amount of the vegetable consumed as fresh (Schieber, et al., 2001 and Ahsan, et al., 2019). Solid waste generated during processing consists mostly of potato peels but also contains green, immature, and cull potatoes and amounts to 15–45% depending on the procedure applied. Several studies suggested the use of water extracts from potato peel for the recovery of antioxidants (Rodriguez et al., 1994). Also, Ibrahim et al., (2004) and Sayed Ahmed, (2016) found that potato skin can play potential roles in protecting the liver disorders and manupulate the complications of diabetes in rats due to its containing of bioactive compounds mainly phenolics and carotenoids with highly antioxidant activities. Mulberry represents one of the less studied plant. It is growing wild in large quantities along waterways, highways and

agricultural roads. Mulberry leaves have been used over the centuries in traditional medicine as a common agent to treat a variety of conditions including diabetes, cardiovascular and cancer diseases through potent antioxidant activity (Butt, et al., 2008). Several studies indicated that mulberry leaves contain many bioactive compounds including minerals, vitamins, flavonoids, phenolics acids, quercetin, isoquercetin and alkaloids (Ewa, et al., 2013; Anastasia-Varvara and Fotini , 2016; Doi, et al., 2001 and Anastasia-Varvara and Fotini , 2016). Such bioactive compounds possesses medical benefits, including diuretic, hypoglycemic, antibacterial, hypotensive properties and neuroprotective functions and anti-obese (Harauma, et al., 2007).

All previous studies confirm the possibility of using these plant parts successfully in the treatment of many diseases including DM. Therefore, the present study was designed to investigate the potential roles of three plant parts (tomato pomace, potato peel and mulberry leaves) and their mixture on oxidant/antioxidant status and hyperglycemia in alloxane-induced diabetic rats.

Materials and Methods

Materials

Plant parts: Tomato and potato fruits were purchased from Benha local markets, Benha City, Benha Governorate. Egypt. Mulberry leaves were obtained by special arrangement with some village farmers lived in of Benha Center, Benha Governorate, Egypt.

Chemicals: Alloxan, used for induction of DM among rats was obtained from Sigma Chemical Co., St. Louis, Mo. Casein, as main source of protein for rat diets preparation purchased from Morgan Company for Chemicals. Cairo, Egypt. Vitamins and salts mixtures, all organic solvents, buffers and other chemicals were of analytical grade were purchased from El-Ghomhorya Company for Trading Drugs, Chemicals and Medical Requirements, Cairo, Egypt.

Methods

Tomato and potato fruits were separated, washed and used for obtaining tomato pomace and potato peels. Tomato pomace, potato peel and mulberry leaves were 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 8%. The dried pomace, peels and leaves were ground into a fine powder in high mixer speed (Moulinex Egypt, ElAraby Co., Benha, Egypt). The material that passed through an 80 mesh sieve was retained for packing in polyethylene pages and storing at 4 ^{0}C until use.

Biological experimental

Animals

Animals used in this study, adult male albino rats (140-150 g per each) were obtained from Helwan Station, Ministry of Health and Population, Helwan, Cairo, Egypt.

Basal Diet

The basic diet for rats feeding was prepared according to the following formula as mentioned by AIN, (1993) as follow: protein, 10%; corn oil, 10%; vitamin mixture, 1%; mineral mixture, 4%; choline chloride, 0.2%; methionine, 0.3%; cellulose, 5% and the remained is corn starch, 69.5%. The used vitamin mixture component was that recommended by Campbell, (1963) while the salt mixture used was formulated according to Hegsted, (1941).

Induction of diabetes

Diabetes was induced in thirty six normal healthy rats by injection into operationally 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 five days fast blood glucose (FBG) was analyzed using a specific kit (AlGomhoryia Company for Trading Drugs, Chemicals and Medical Instruments, Cairo, Egypt) by a drop of

blood was obtained from tail vein and subjected to a strip of haemogluco test. All rats with FBG >126 mg/dl were considered to be diabetics and included in the study.

Experimental design

All biological experiments performed complied with the rulings of the Institute of Laboratory Animal Resources, Commission on life Sciences, National Research Council (NRC, 1996). Rats (n=36 rats), were housed individually in wire cages in a room maintained at 25 ± 2 ^{0}C and kept under normal healthy conditions. All rats were fed on basal diet for one-week before starting the experiment for acclimatization. After one week period, the rats were divided into two main groups, the first group (Group 1, 6 rats) still fed on basal/standard diet (SD) and the other main group (30 rats) was used for diabetes induction and classified into five sub groups as follow: group (2), fed on standard diet only as a positive control (rats with diabetes); group (3), fed on SD containing 5 % (w/w) MLP; group (4), fed on SD containing 5 % (w/w) TPP; group (5), fed on SD containing 5 % (w/w) PPP and group (6), fed on SD containing 5 % (w/w) mix (mixture of MLP, TPP and PPP by equal parts).

Blood sampling

At the end of experiment period, 28 days, blood samples were collected after 12 hours fasting using the abdominal aorta and rats were scarified under ether anesthetized. Blood samples were received into glass centrifuge tubes, containing oxalate solution (1.34 %) as anticoagulant. After centrifugation at 3000 rpm for 10 min., plasma was with drown and used for the analysis of vitamins. The erythrocyte residue was washed with three successive portions of sodium chloride solution (0.9 %) and then haemolysed with deionised water for 30 min. Haemolysate was then centrifuged at 30,000 rpm for 30 min. and the supernatant fractions was transferred to a clean test tube and analyzed of antioxidant enzymes (Stroev and Makarova, 1989). Liver organ was removed and used for GSH and MDA determination.

Hematological analysis

Different tested parameters in serum were determination using specific methods as follow: glutamic oxaloacetic transaminas (AST), glutamic pyruvic transaminas (ALT), and alkaline phosphatase (ALP) activities according to Yound, (1975); Tietz, (1976) and Yound, (1975), respectively. Enzymatic determination of plasma glucose was carried out colorimetrically according to Yound, (1975) and Tietz, (1976).

Glutathione (GSH) determination in liver tissue

Reduced glutathione (GSH) in liver tissue was determined according to the method of McFarris and Reed ,(1987). Samples were prepared, extracted, purified, derivatized and injected onto HPLC system (SP Thermo Separation Products Liquid Chromatograph (Thermo Separation products, San Jose, CA).

Malonaldehyde content (MDA)

Lipid peroxide levels measured as malonaldehyde (MDA) in liver tissues samples were determined by as thiobarbituric acid reactive substances (TBARS) as described by Stroev and Makarova, (1989). The absorbance (Abs) of the samples was compared to a standard curve of known concentrations of malonaldialdehyde by using Labo-med. Inc., spectrophotometer, CA.

Antioxidant enzymes (GSH-Px, GSH-Rd, CAT and SOD)

Glutathione peroxidase (GSH-Px) and catalase (CAT) activities were measured as described by Splittgerber and Tappel, (1979) and Aebi, 1974, respectively. Superoxide dismutase (SOD) activity was measured by Ransod kit (Randox laboratories mmited, Germany). Glutathione reductase (GSH-Rd) activity was determined according to the method recommended by the International Committee for Standardization in Haematology (ICSH, 1979).

Antioxidant vitamins (A, C, and E)

Vitamins A, E (α-tocopherol) and C (ascorbic acid) were extracted and analysed by HPLC techniques according to the methods of Epler, et al., (1993), Hung, et al., (1980), and Moeslinger, et al., (1994), respectively. Quantitative

determination of each vitamin was determined from its respective peak area and corresponding response factor. The percent recoveries of vitamins were also studied by adding each vitamin to serum after sample preparation and HPLC determination. Under such methods chromatographic conditions, the Mean ±SD values of vitamins A, C and E recoveries were 91.45 ± 3.61, 87.56 ± 2.49, and 85.67 ± 3.56, respectively.

Statistical Analysis

All measurements were done in triplicate and recorded as mean±SD. Statistical analyses were performed using Student t-test and MINITAB 12 computer program statistical software (Minitab Inc., State College, PA). **P** values ≤ 0.05 were considered significant.

Results and Discussion

The effect of selected plant parts on serum glucose of diabetic rats

Data in Table (1) and Figure (1) were shown the effect of selected plant parts on serum glucose concentration of alloxane-induced diabetic rats. Such data indicated that treatment of rats with alloxan caused a significant increased ($p \leq 0.01$) in serum glucose concentration by the ratio 113.48% compared to normal controls. Supplementation of the rat diets with 5% of the selected plant parts including MLP, TPP, PPP and their mixture leads to decrease this value by the rate of -18.25, -23.20, -20.93 and -26.80%, respectively. The mixture treatment gave maximum hypoglycemic yield followed by TPP, PPP and MLP. It could be mean that a combination of different selected plant parts may be more efficient for reducing the serum glucose level because the interactive effects occurred by different categories of bioactive compounds of the selected plant parts used.

All of our data reported that MLP, PPP and TPP display potent hypoglycemic action in alloxan-induced diabetic rats. Such activity may be related to diverse bioactive compounds present in tomato pomace, potato peel and mulberry leaves. For example, Farzad ,et al., (2011) found that tomatoes are a rich source of

lycopene, β-carotene, vitamin C, flavonoids, folate and vitamin E that may provide protection against the development of T2DM patients. They also reported that consumption of 200 g raw tomato per day had a favored effect on blood pressure and apoA-I so it might be beneficial for reducing cardiovascular risk associated with T2DM. Also, Ibrahim, et al., (2004) and Sayed Ahmed, (2016) found that potato skin can play potential roles in protecting the liver disorders and manupulate the complications of diabetes in rats due to its containing of bioactive compounds mainly phenolics and carotenoids with highly antioxidant activities. Furthermore, several studies indicated that mulberry leaves contain many bioactive compounds including minerals, vitamins, flavonoids, phenolics acids, quercetin, isoquercetin and alkaloids (Doi, et al., 2001; Ewa, et al., 2013 and Anastasia-Varvara and Fotini , 2016). Such bioactive compounds possesses medical benefits, including diuretic, hypoglycemic, antibacterial, hypotensive properties and neuroprotective functions and anti-obese (Harauma, et al., 2007). Another studies indicated that such bioactive compounds found in the selected plant parts are known for their properties in scavenging free radicals, inhibiting lipid oxidation in vitro and improve glucose response and insulin resistance associated with type 2 diabetes (Noda, et al., 2002 and Jung, et al., 2011).

The effect of selected plant parts on serum liver functions of diabetic rats

The effect of selected plant parts on serum liver functions enzymes activities (aspartate aminotransferase, AST, alanine aminotransferase, ALT and alkaline phosphatase, ALP) of diabetic rats induced by alloxan were shown in Table (2) and Figure (2). Such data indicated that treatment of rats with aloxane caused a significant increased ($p \leq 0.05$) in AST, ALT and ALT with 29.21, 26.62 and 57.29% compared to normal control group, respectively. Supplementation of the rat diets with 5% of the selected plant parts including MLP, TPP, PPP and their mixture leads to decrease

Table 1. The effect of selected plant parts on serum glucose concentration (mg/dL) of diabetic rats induced by alloxan *

Value	Control (ve-) Std diet	Control (ve+) Diabetic	Plant parts (5%, w/w)			
			MLP	TPP	PPP	Mix
Mean	92.56 d	197.60 a	161.54 b	151.76 bc	156.25 b	144.65 c
SD	4.22	8.2	5.22	4.1	4.24	5.7
% of Change	0.00	113.48	-18.25	-23.20	-20.93	-26.80

*MLP, mulberry leaves powder; TPP, tomato pomace powder; PPP, potato peel powder and Mix, mixture of MLP, TPP and PPP by equal parts. Means in the same row with different letters are significantly different at $p \leq 0.01$.

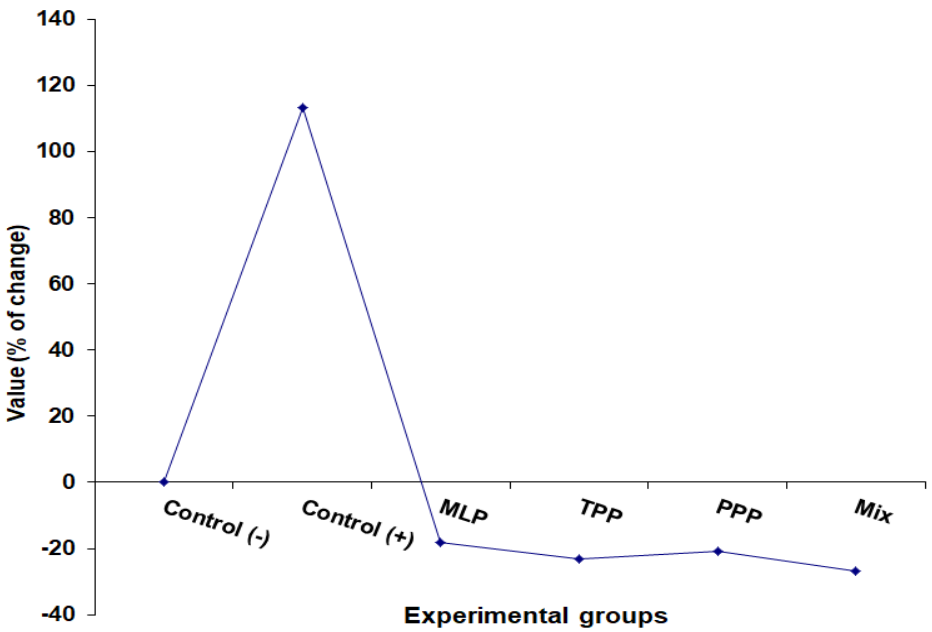

Figure 1. The effect of selected plant parts on serum glucose concentration of diabetic rats induced by alloxan *

*MLP, mulberry leaves powder; TPP, tomato pomace powder; PPP, potato peel powder and Mix, mixture of MLP, TPP and PPP by equal parts.

these values by the rate of -9.72, -13.00, -10.76 and -16.03%; -11.23, -14.14, -12.73 and -15.72%; and -10.10, -23.28 , -20.16 and -26.85%, respectively. The mixture treatment gave maximum reduction yield of liver functions enzymes activities followed by TPP, PPP and MLP. It could be mean that a combination of

different selected plant parts may be more efficient for reducing the serum liver functions enzymes activities because the interactive effects probably occurred by different categories of bioactive compounds reported in the selected plant parts used.

Aminotransferases (ALT and AST) plus ALP are normally intracellular enzymes. Thus, the presence of elevated levels of aminotransferase and ALP in the plasma indicates damage to cells rich in these enzymes. For example, physical trauma or a disease process can cause cell lysis resulting release of intracellular enzymes into the blood (Pagana and pagana, 1997). The effect of plant parts powders/extracts on decreasing the serum liver function enzymes activity have been reported by many studies (El-Nashar, 2007; Elhassaneen , et al., 2013; Sayed Ahmed, 2016; Elmaadawy, 2016 and Aly, et al., 2017). Such effects could be attributed to their high level content of bioactive compounds. Several previous studies reported that the selected plant parts (MLP, PPP and TPP) are rich by different classes of phytochemicals including phenolics, anthocyanins, flavonols, lycopene, carotenoids and alkaloids (Anastasia-Varvara and Fotini , 2016; Sayed-Ahmed, 2016 and Aly, et al., 2017). Such bioactive compounds could be lowered liver serum enzymes through many actions including phenolic compounds are known to block the hepatocellular uptake of bile acids and improved the antioxidant capacity of the liver, diminished the bilirubin concentration reduce the damage of hepatocytes, scavengers of reactive oxygen species (Beattic, et al., 2005; Sayed Ahmed, 2016; and Mahran , et al., 2018)

Table 2. The effect of selected plant parts on serum liver functions of diabetic rats induced by alloxan**.**

Value	Control (ve-) Std diet	Control (ve+) Diabetic	Plant parts (5%, w/w)			
			MLP	TPP	PPP	Mix
Serum alanine aminotransferase (ALT,U/L)						
Mean	27.56 [c]	35.61 [a]	32.15 [a]	30.98 [ab]	31.78 [a]	29.90 [b]
SD	4.67	6.32	4.89	7.12	5.21	4.16

% of Change	0.00	29.21	-9.72	-13.00	-10.76	-16.03
Serum aspartate aminotransferase (AST,U/L)						
Mean	44.67 ^{c}	56.56 ^{a}	50.21 ^{ab}	48.56 ^{b}	49.36 ^{ab}	47.67 ^{b}
SD	6.32	5.27	9.38	6.38	8.91	11.25
% of Change	0.00	26.62	-11.23	-14.14	-12.73	-15.72
Serum alkaline phosphatase (ALP,U/L)						
Mean	162.34 ^{d}	255.34 ^{a}	229.54 ^{b}	195.89 ^{c}	203.87 ^{c}	186.78 ^{d}
SD	15.23	33.24	9.05	9.80	12.67	1.80
% of Change	0.00	57.29	-10.10	-23.28	-20.16	-26.85

*MLP, mulberry leaves powder; TPP, tomato pomace powder; PPP, potato peel powder and Mix, mixture of MLP, TPP and PPP by equal parts. Means in the same row with different letters are significantly different at $p \leq 0.05$.

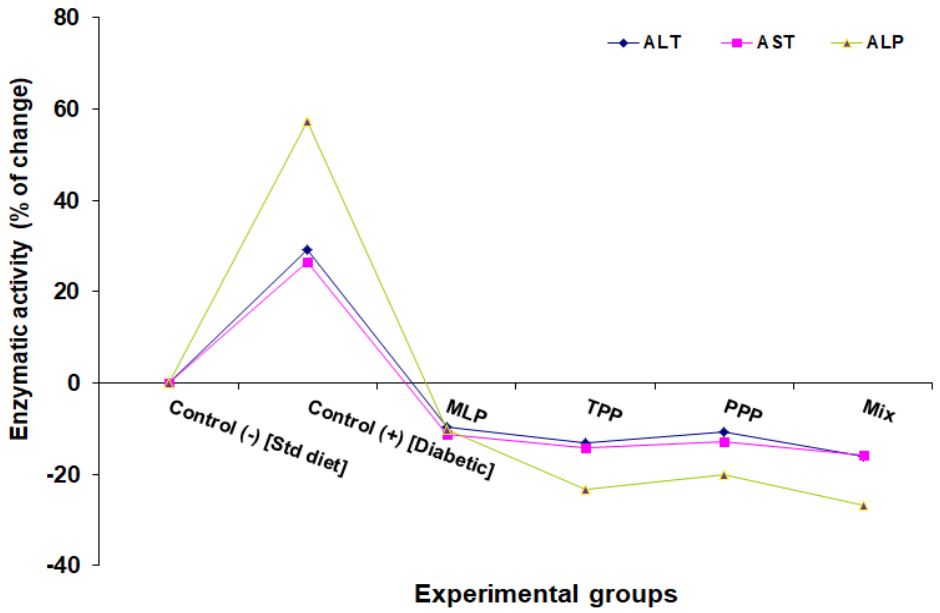

Figure 2. The effect of selected plant parts on serum liver functions of diabetic rats induced by alloxan*

*MLP, mulberry leaves powder; TPP, tomato pomace powder; PPP, potato peel powder and Mix, mixture of MLP, TPP and PPP by equal parts.

The effect of selected plant parts on antioxidant status of diabetic rats

Reduced glutathione (GSH) concentration in liver tissue

The effect of selected plant parts on reduced glutathione (GSH) concentration in liver tissue of alloxan-induced diabetic rats were shown in Table (3) Figure (3). Such data indicated that treatment of rats with aloxan caused a significant decreased ($p \leq 0.05$) in liver GSH content (-32%) compared to normal/control group. Supplementation of the rats diets with 5% of the selected plant parts including MLP, TPP, PPP and their mixture leads to increase this value by the rate of 12.54, 23.94, 14.82 and 28.34%, respectively. So, the increasing in liver GSH content was depending on the type of the selected plant parts applied in the diets. The highest content of the biological antioxidant (GSH) was recorded for applying the mixture of the selected plant parts extracts followed by TPP, PPP and MLP, respectively. It could be mean that a combination of different selected plant parts may be more efficient for increasing the liver GSH level because the interactive effects occurred by different categories of bioactive compounds of the selected plant parts used. In similar studies, marked decreased level of GSH is reported in the plasma/liver of diabetic patients/animals (Sayed Ahmed, 2016). GSH systems/roles may have the ability to manage oxidative stress with adaptation changes in enzymes regulating GSH metabolism i.e link between hyperglycemia and GSH depletion (Lee ,et al., 1995).

Table 3. The effect of selected plant parts on reduced glutathione concentration (GSH, µmol / mg tissue protein) in liver tissue of diabetic rats induced by alloxan *

Value	Control (ve-) Std diet	Control (ve+) Diabetic	Plant parts (5%, w/w)			
			MLP	TPP	PPP	Mix
Mean	9.03 [a]	6.14 [c]	6.91 [b]	7.61 [ab]	7.05 [b]	7.88 [ab]
SD	1.86	2.27	1.87	1.52	2.11	1.46
% of Change	0.00	-32.00	12.54	23.94	14.82	28.34

*MLP, mulberry leaves powder; TPP, tomato pomace powder; PPP, potato peel powder and Mix, mixture of MLP, TPP and PPP by equal parts. Means in the same row with different letters are significantly different at p≤0.05.

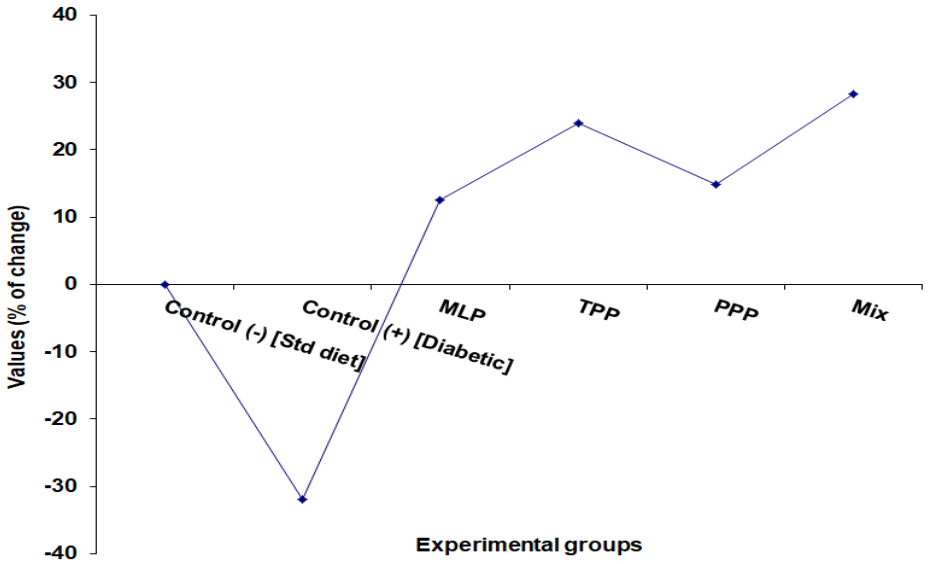

Figure 3. The effect of selected plant parts on reduced glutathione concentration in liver tissue of diabetic rats induced by alloxan*

*MLP, mulberry leaves powder; TPP, tomato pomace powder; PPP, potato peel powder and Mix, mixture of MLP, TPP and PPP by equal parts.

They also reported that hyperglycemia is the cause of GSH depletion. So, data of the present study reported that feeding the diabetics rats with selected plant parts (MLP, TPP and PPP) significantly removed some of the metabolic disorders induced by diabetes in liver cells through increasing the GSH synthesis. Several studies reported the potent antioxidant capacities of those plant parts and other in both in vitro and in vivo systems (Ewa, et al., 2013; Sayed Ahmed, 2016; and Aly, et al., 2017). Such effect leads to increase GSH and stimulate its related antioxidant enzymes system including GSH-Px and GSH-Rd (Fayez, 2016 and Mahran, et al., 2018). Also, Sharma and Maguer, (1996) lycopene is the principal carotenoids causing the characteristic red hue of tomatoes and most of it is associated with the water-insoluble fraction and the skin. Lycopene is an especially powerful antioxidant because its multiplicity of conjugated double bonds makes it a good quencher of free radicals. It is also usually

one of the most common carotenoids in the blood serum. Therefore, it can be an important part of the antioxidant defense system and may function as an anticancer agent, lower heart disease risk and inhibits cholesterol oxidation/synthesis (Betty, 2002).

Antioxidant enzymes activities in red blood cells (RBCs)

The effect of selected plant parts on erythrocytes antioxidant enzymes activities including GSH-Px, GSH-Rd, CAT and SOD of diabetic rats induced by alloxan were shown in Table (4) and Figure (4). Such data it could be noticed that diabetes induced a significant ($p \leq 0.05$) decreased in GSH-Px, GSH-Rd, CAT and SOD activities of RBC's by a rates of -37.93, -17.87, -21.62 and -36.66% compared to normal/control group, respectively. Supplementation of the rat diets with 5% of the selected plant parts (MLP, TPP, PPP and their mixture) increased GSH-Px, GSH-Rd, CAT and SOD activities which recorded 15.08, 35.79, 26.47 and 39.55%; 4.90, 10.93, 7.97 and 15.38%; 9.11, 15.37, 13.13 and 25.26%; and 16.36, 31.82, 18.48 and 38.48%, respectively. The highest activation was recorded with the mixture treatment followed by TPP, PPP and MLP, respectively. It could be mean that a combination of different selected plant parts may be more efficient for elevating the RBC's antioxidant enzymes activities, the biomarkers of enhancing the antioxidative status RBC's, due to the interactive effects occurred by different categories of bioactive compounds of plant parts applied. The present data are in accordance with that mentioned by Elmaadawy, et al., 2016).

In general, different organisms have developed antioxidant defenses systems largely based on antioxidant enzymes able to scavenge reactive oxygen species subsequently prevent their effects in cellular damages. Among of these enzymes SODs are 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, GSH-Rd enzyme catalyze the reaction: $GSSG + NADPH + H^+ \rightarrow 2GSH + NADP^+$ (Thomas ,et al., 1990). Several studies reported that antioxidant enzymes systems are active in liver cells (Galinier, et al., 2004 and Cao, 2014). Decreasing the activity of the antioxidant

enzyme or its invalidation in animals results in increased reactive oxygen species production and mitochondrial dysfunction (Curtis, et al., 2010). The selected plant parts feeding to animals are rich in bioactive compounds such phenolics, , carotenoids , alkaloids, lycopene etc which exhibited antioxidant activities in different biological systems (Mashal, 2016; and Sayed Ahmed, 2016; and Aly, et al., 2017). Such antioxidant properties are important in manipulation of the diabetes development through increasing the antioxidant enzymes activities which is one of the mechanisms of anti-oxidation in RBC's.

Table 4. The effect of selected plant parts on erythrocytes antioxidant enzymes activities of diabetic rats induced by alloxan[*].

Value	Control (ve-) Std diet	Control (ve+) Diabetic	Plant parts (5%, w/w)			
			MLP	TPP	PPP	Mix
Glutathione peroxidase (GSH-Px, U/g Hb)						
Mean	24.89 [a]	15.45 [c]	17.78 [b]	20.98 [ab]	19.54 [ab]	21.56 [a]
SD	1.78	1.91	1.87	2.96	2.02	2.11
% of Change	0.00	-37.93	15.08	35.79	26.47	39.55
Glutathione reductase (GSH-Rd, U/g Hb)						
Mean	10.69 [a]	8.78 [b]	9.21 [a]	9.74 [a]	9.48 [a]	10.13 [a]
SD	1.53	0.82	1.16	1.07	1.52	2.27
% of Change	0.00	-17.87	4.90	10.93	7.97	15.38
Catalase (CAT, U/g Hb)						
Mean	182.67 [a]	143.18 [c]	156.23 [bc]	165.19 [b]	161.98 [b]	179.35 [a]
SD	17.89	10.18	14.55	24.02	20.56	15.20
% of Change	0.00	-21.62	9.11	15.37	13.13	25.26
Superoxide dismutase (SOD, U/g Hb)						
Mean	5.21 [a]	3.30 [b]	3.84 [b]	4.35 [a]	3.91 [b]	4.57 [a]

SD	1.11	0.66	1.21	0.29	1.22	1.43
% of Change	0.00	-36.66	16.36	31.82	18.48	38.48

*MLP, mulberry leaves powder; TPP, tomato pomace powder; PPP, potato peel powder and Mix, mixture of MLP, TPP and PPP by equal parts. Means in the same row with different letters are significantly different at $p \leq 0.05$.

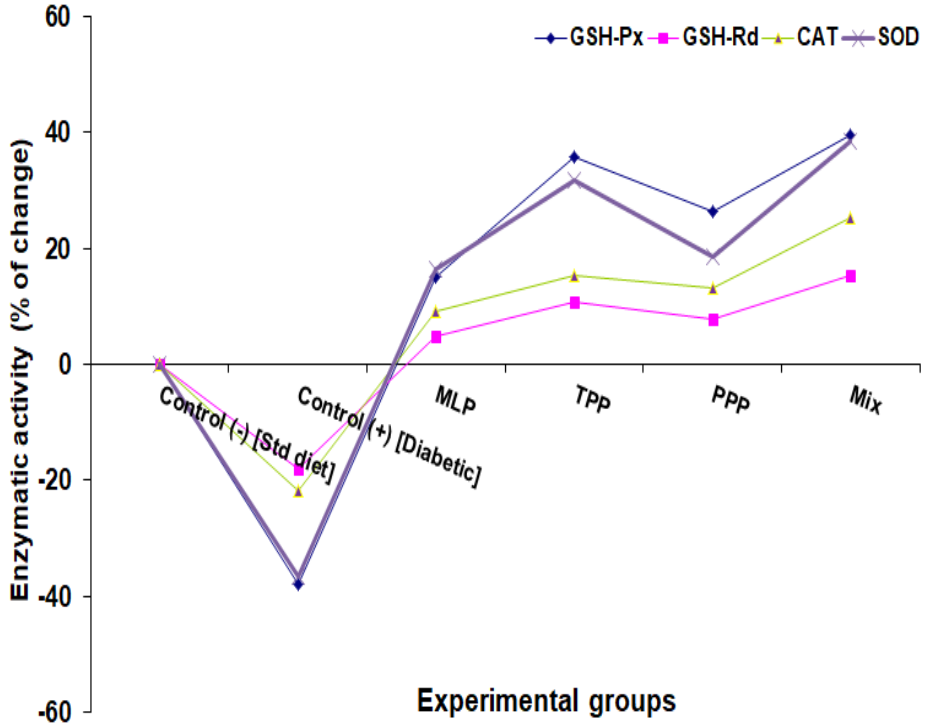

Figure 4. The effect of selected plant parts on erythrocytes antioxidant enzymes activities of diabetic rats induced by alloxan*

*MLP, mulberry leaves powder; TPP, tomato pomace powder; PPP, potato peel powder and Mix, mixture of MLP, TPP and PPP by equal parts.

Antioxidant vitamins concentration in plasma

The effect of selected plant parts on plasma antioxidants vitamins concentration of diabetic rats induced by alloxan were shown in Table (6) and Figure (6). From such data it could be noticed that diabetes induced a significant ($p \leq 0.05$) decreased in vitamins A, C and E concentration in plasma by a rates of -18.71, -27.17 and -30.46% compared to normal/control group, respectively. Supplementation of the rat diets with 5% of the selected plant parts (MLP, TPP, PPP and their mixture) increased the concentrations of vitamins A, C and E which recorded 3.54, 11.50, 7.08 and 15.04%; 7.40, 19.67, 13.36 and 25.18; and 12.83, 23.07, 16.06 and 33.73%, respectively. The highest concentration was recorded with the mixture treatment

Table 6. The effect of selected plant parts on Plasma antioxidants vitamins concentration of diabetic rats induced by alloxan**.**

Value	Control (ve-) Std diet	Control (ve+) Diabetic	Plant parts (5%, w/w)			
			MLP	TPP	PPP	Mix
Vitamin A (Retinol, □mol/L)						
Mean	1.39 [a]	1.13 [bc]	1.17 [b]	1.26 [a]	1.21 [b]	1.30 [a]
SD	0.16	0.16	0.19	0.22	0.14	0.21
% of Change	0.00	-18.71	3.54	11.50	7.08	15.04
Vitamin C (Ascorbic acid, □mol/L)						
Mean	64.23 [a]	46.78 [c]	50.24 [b]	55.98 [b]	53.03 [b]	58.56 [ab]
SD	3.13	6.02	5.6376	4.5252	7.668	5.23
% of Change	0.00	-27.17	7.40	19.67	13.36	25.18
Vitamin E (Tocopherol, □mol/L)						
Mean	31.16 [a]	21.67 [b]	24.45 [ab]	26.67 [ab]	25.15 [ab]	28.98 [ab]
SD	4.10	5.20	1.87	4.43	3.52	2.89
% of Change	0.00	-30.46	12.83	23.07	16.06	33.73

*MLP, mulberry leaves powder; TPP, tomato pomace powder; PPP, potato peel powder and Mix, mixture of MLP, TPP and PPP by equal parts. Means in the same row with different letters are significantly different at p≤0.05.

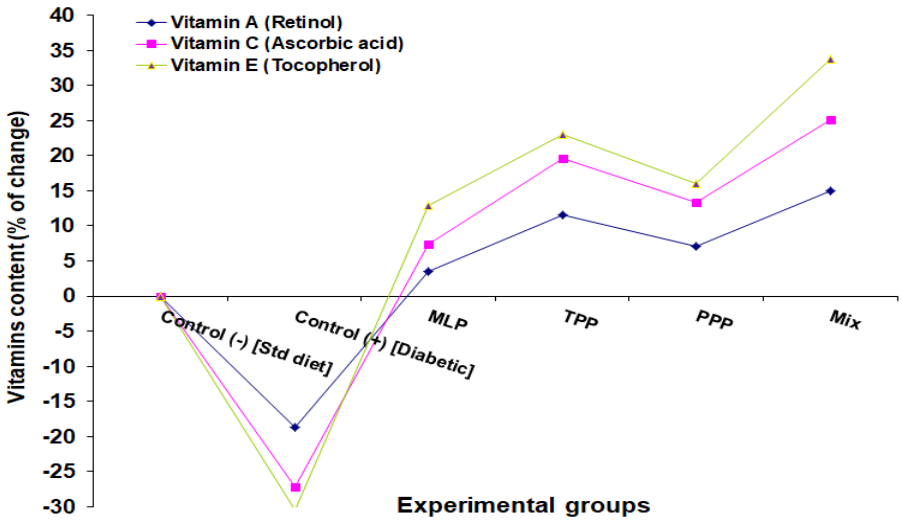

Figure 6. The effect of selected plant parts on Plasma antioxidants vitamins concentration of diabetic rats induced by alloxan**.**

*MLP, mulberry leaves powder; TPP, tomato pomace powder; PPP, potato peel powder and Mix, mixture of MLP, TPP and PPP by equal parts.

followed by TPP, PPP and MLP, respectively. It could be mean that a combination of different selected plant parts may be more efficient for elevating the plasma antioxidant vitamins concentrations, the biomarkers of enhancing the antioxidative status in plasma, due to the interactive effects occurred by different categories of bioactive compounds of plant parts applied. Generally, plasma is rich in natural non-enzymatic antioxidants such lipid soluble vitamins (e.g., vitamins A and E) or β-carotenoids (Wohaieb and Godin, 1987 and Voet and Voet, 1990). Present data with the others indicated that selected plant parts and their mixtures feeding are rich in bioactive compounds including vitamins which exhibited antioxidant activities in different biological systems (Mashal, 2016; Sayed Ahmed, 2016 and Aly, et al., 2017). Such antioxidants properties are important in manipulation of the diabetes development through scavenging of the reactive oxygen species subsequently increase the bioavailability of the vitamins in cells plasma.

The effect of selected plant parts on malonaldehyde concentration in liver tissue of diabetic rats

The effect of selected plant parts on malonaldehyde concentration (MDA) in liver tissue of alloxan-induced diabetic rats were shown in Table (7) and Figure (7). Such data indicated that treatment of rats with alloxan caused a significant increased ($p \leq 0.05$) in liver MDA content (35.06%) compared to normal/control group. Supplementation of the rats diets with 5% of the selected plant parts including MLP, TPP, PPP and their mixture leads to decrease this value by the rate of -10.21, -12.34, -11.06 and -19.15%, respectively. So, the decreasing in liver MDA content was depending on the type of the selected plant parts applied in the diets. The lowest content of the biological oxidant (MDA) was recorded for applying the mixture of the selected plant parts extracts followed by TPP, PPP and MLP, respectively. Such data mean that a combination of different plant parts may be more efficient for reducing liver tissue MDA level, the biomarkers of oxidative stress in liver, due to the interactive effects probably occurred by different categories of bioactive compounds in the selected of plant parts. The present data are in

accordance with that observed by Jung, et al., (2011) who reported that oxidative stress and metabolic dysregulation of free fatty acids in diabetes were alleviated by onion peel extract (contain the same bioactive compound found in the selected plant parts) administration. Also, Aly, et al., (2017) hepatic oxidant stress was reduced by tomato pomace extract as assessed by decreasing the oxidation in LDL y and MDA formation. Furthermore, Jacob and Burri, (1996) reported that the antioxidant defense system of other bioactive compounds found in tomato pomace including vitamins (C and E), minerals (Cu and Se), phytonutrients (lutein and β-carotene,), and biological products (coenzyme Q10 and bilirubin) that protect tissues from oxidative stress damage. Therefore, the present data hypothesis that the selected plant parts feeding lead to improve insulin secretion/sensitivity, at least in part, through enhancing lipid metabolism and reducing oxidative stress in diabetic rats.

Correlation studies

In the correlation analysis, important differences were found between oxidative stress parameters (MDA) and antioxidant defense systems [enzymatic (GSH-Px, GSH-Rd, CAT and SOD) and non-enzymatic (GSH, and vitamins A, C and E)] in diabetic rats feeding selected plant parts (MLP, TPP and PPP and their mixture) (Table 8). From such data it could be noticed that there was a strong negative

Table 7. The effect of selected plant parts on malonaldehyde concentration (MDA, nmol/mg tissue protein) in liver tissue of diabetic rats induced by alloxan *

Value	Control (ve-) Std diet	Control (ve+) Diabetic	Plant parts (5%, w/w)			
			MLP	TPP	PPP	Mix
Mean	0.174 ^{d}	0.235^{a}	0.211 ^{ab}	0.206 ^{b}	0.209 ^{b}	0.190 ^{c}
SD	0.025	0.142	0.071	0.051	0.043	0.061
% of Change	0.00	35.06	-10.21	-12.34	-11.06	-19.15

*MLP, mulberry leaves powder; TPP, tomato pomace powder; PPP, potato peel powder and Mix, mixture of MLP, TPP and PPP by equal parts. Means in the same row with different letters are significantly different at p≤0.05.

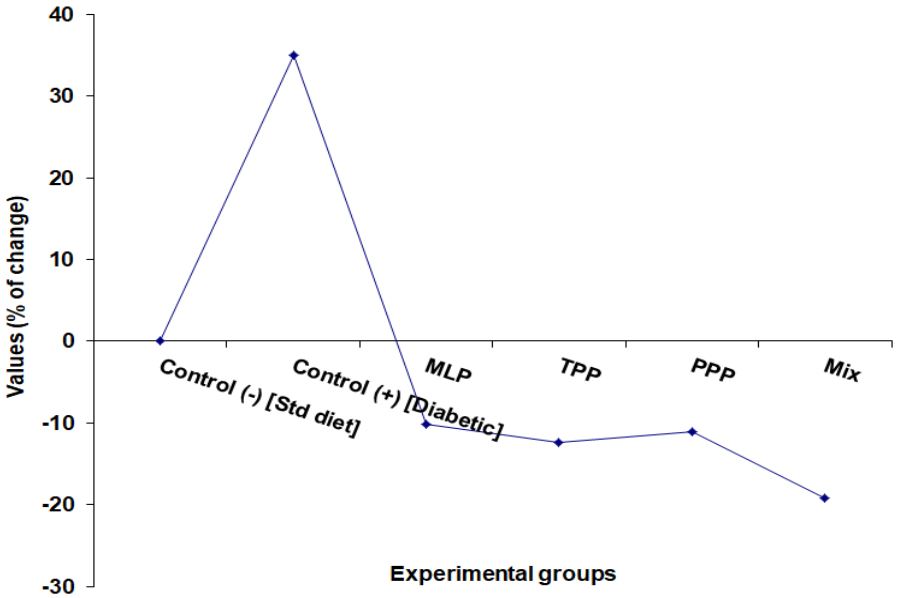

Figure 7. The effect of selected plant parts on malonaldehyde concentration (MDA, nmol/mg tissue protein) in liver tissue of diabetic rats induced by alloxan *

*MLP, mulberry leaves powder; TPP, tomato pomace powder; PPP, potato peel powder and Mix, mixture of MLP, TPP and PPP by equal parts.

significant (p≤ 0.05) relationship between MDA in the liver tissues and GSH concentration in liver (r^2 = - 0.935), antioxidant enzymes in RBC's [GSH-Px (r^2 = - 0.912), GSH-Rd (r^2 = -0.825), CAT (r^2 = - 0.849) and SOD (r^2 = - 0.824)] and antioxidant vitamins in plasma [vitamin A (r^2 = - 0.757), vitamin C (r^2 =- 0.629) and vitamin E (r^2 = - 00.786)]. The correlation data of the present study indicated that the reducing in antioxidant enzymes (GSH-Px, GSH-Rd, SOD and CAT) defense potential of RBC's was contrary with significant decreasing (p≤0.05) in antioxidant vitamins (A, C and E) in rats plasma as a consequence of diabetes injury. By other meaning, these correlations confirm that if there were no change in the antioxidant defense systems of diabetes rats, it would be difficult to observe high concentrations of MDA.

In similar study, Bohm ,et al., (1997) in some model systems noticed a combination of vitamins E and A interact synergistically to inhibit lipid peroxidation i.e. increased MDA. Also, Shalaby, (2014) reported that high levels of lipid peroxidation i.e. MDA in the plasma of diabetic rats were associated with rather low levels of enzymatic and non-enzymatic antioxidant**s.** Furthermore, Elmaadawy, (2016) found that increasing in MDA concentrations are associated with low level of GSH in the plasma of diabetic rats.

Table 8. Correlation between oxidative stress and antioxidant defense systems in diabetes rats feeding the selected plant parts*

Parameters	**r^{2*}**	**Parameters**	**r^2**
MDA/GSH	- 0.935	MDA/SOD	- 0.824
MDA/GSH-Px	- 0.912	MDA/ Vit A	- 0.757
MDA/GSH-Rd	-0.825	MDA/Vit C	- 0.629
MDA/CAT	- 0.849	MDA/Vit E	- 0.786

* $P \leq 0.05$

In conclusion, data of the present study has demonstrated the efficiency of the selected plant parts including mulberry leaves, tomato pomace, potato peel and their mixture to partially ameliorate hyperglycemia and its complications in diabetic rats. All of these treated effects could be attributed to the high contents of many bioactive compound categories found in the tested plant parts which exhibited high antioxidant activities. These antioxidant activities affect the oxidants (oxidative stress) formation as the diabetes development through different mechanisms of action including: 1) increasing the GSH synthesis, 2) stimulate antioxidant enzymes activities, and 3) increasing the antioxidant vitamins levels in the living cells. These findings provide a basis for the use of the selected plant parts for the prevention and/or treatment of type-2 diabetes.

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