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THE ANTIOXIDANT EFFECT OF NATURAL POLYPHENOLIC COMPLEXES OF GRAPE WINE IN THE RAT KIDNEYS UNDER STREPTOZOTOCIN-INDUCED DIABETES MELLITUS

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The possible protective effect of the speciment of natural polyphenols complexes of grape wine in the kidneys of white rats under streptozotocin-induced diabetes mellitus, which is reflected in the activation of enzyme antioxidant system and reduced pathogenic actions of reactive oxygen species underlying the mechanisms of various diabetic diseases, separately diabetic nephropathy is discussed in this scientific article.

Key words: diabetes mellitus, polyphenolic complexes, diabetes nephropathy, oxidative stress, antioxidant protection.

Diabetes mellitus is one of the most common, not infections diseases, which are characterized by the development of micro and macro vascular complications, that can lead to disability.

Diabetes is characterized by the lack of energy substrates, that activate free radical oxidation. This causes increase in the cytotoxic properties of reactive oxygen species (ROS) and it is one of the causes of oxidative stress (OS).

In 2005 unified theory of diabetic damage was formulated by Michael Brownlee. It is base on polyol, hexosamine pathway, protein kinase C (PKC) pathway and not enzymic glucose utilization through the accumulation of advanced glycated end-products (AGEs) [14]. Activation of these pathways leads to the increaseing not enzymic glycosylation that is high even under conditions of diabetes. Under interaction of AGEs with specific receptors for them (RAGES), activation of the cascade of mechanisms that leads to take place the increased gene expression, that encode a number of preinflammatory cytokines (TNF-α, IL 1,6), vasoconstrictors – endothelin 1, adhesion molecules (ICAM-1, VCAM-1) and growth factors. They violate the function of blood vessels and contribute to premature development of atherosclerosis and inflammatory processes [24, 26], induce super activity of locally-renal renin-angiotensin system [13], help to increase blood pressure and glomerular filtration rate, etc. The last injuries cause the development of microalbinyria and microproteinyria. Accordingly, we can assume that effect of OS and AGEs in the main lead to the development of diabetic nephropathy (DN).

Diabetic nephropathy – is the specific disease that is accompanied by the formation of glomerular and diffuse glomerulosclerosis. Its terminal stage is characterized by the development of chronic renal failure [13]. Diabetic nephropathy occurs as a result of a complex variety of pathological processes which are formed primarily in the capillaries and small vessels of the kidneys. Like all microangiopathies, this disease is realized through the emergence and progression of endothelial dysfunction.

As we know, kidney glomeruls consist of endotheliocytes that cover the capillaries from the inside, podocytes that cover the capillaries from the outside, providing a filter barrier and mesangial cells which are elements of smooth muscle tissue that are located around the capillaries and involved in the regulation of blood flow velocity [2]. Experimental Diabetes Mellitus (EDM)

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is characterized by podocytes apoptosis that is accompanied by a sharp decrease in their number. All changes leading to thicking of the filtering barrier with involving of proteins, in particular, collagen IV with further progression of fibrogenesis until the complete loss of physiological function of glomerular [2]. That's why inflammatory processes in the glomerulus are accompanied by increase in the body size and weight [19].

Under DM part of the "strike" is taken by enzymatic antioxidant system of the body, that under this disease is characterized by reducing of its activity [*7*]. Therefore, the survey of natural antioxidants – natural polyphenols complexes of grape which have the effect of preventing cardiovascular diseases was become actual recently [21]. As we know, polyphenols complexes can interact with plasma proteins and cellular elements of blood, prevent premature oxidation of the molecular structures of their complexes. A significant bactericidal and antiviral effect of the given substances is also shown [15].

As protective properties of natural grape polyphenols complexes under streptozotocin-induced diabetes mellitus and their affect on enzymic antioxidant system under development of nephropathy were investigated little, the goal of our work was to investigate the protective antioxidant effect of speciment of polyphenols complexes on enzymatic antioxidant system in kidney tissue of white rats under streptozotocin-induced diabetes mellitus.

Materials and methods

All animal care and procedures were carried in accordance with the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes Directive of 24 November 1986 (86/609/ECC) and were approved by Bioethics Committee of Ivan Franko National University of Lviv Protocol for Animal Studies, Lviv, Ukraine. Male Wistar rats, of 120–150 g body weight, were fed a standard rat chow and had access to water ad libitum.

Speciment of natural polyphenols complexes of grape wine (speciment) was received by evaporation of red wine in rotary evaporators LABOROTA 4000 (Heidolph, Germany).

The red wine was made by the classical technology from Cabernet Sauvignon grapes and contained phenolic compounds 2309.31 mg/l, proanthocyanidines 936.0 mg/l and pigment polymers 443.8 mg/l.

Wistar rats were separated into four groups each of seven animals: Group 1 – normal untreated control; Group 2 –speciment of polyphenols treated;Group 3 – STZ treated and Group 4 – speciment of polyphenols and STZ treated. The STZ treatment was a single i.p. injection of 50 mg/kg body weight. The red wine treatment was (an oral dose of 23,5 mg/kg body weight/day, based on the proportion of 300 ml wine/70kg body weight/day) administered daily for 2 weeks prior to the STZ injection and daily for 4 weeks after the STZ injection. Group 2 received red wine for 6 weeks. Blood samples for glucose measurements were taken from the tail vein ,72 h after the STZ injection and the day prior to the study termination. All rats with blood glucose of 14 mmol/l or more were considered diabetic.

The animals were sedated by CO_2 and immediately killed by cervical dislocation. Selected tissues were frozen immediately in liquid nitrogen. Tissues homogenization was carried out using hand homogenizers in the presence of 0,1 M phosphate buffer (1:10 wt/vol) pH 7,0 on the ice. The homogenate was centrifuged at 10620 g for 15 min. All the aforementioned steps were done at 4°C.

The activity of superoxide dismutase (SOD) was determined by the method of Chevari [12], catalase – by the Corolyk [6], glutathione peroxidase – by the Moin [9], glutathione reductase – by the Goldberg [16]. MDA level analyzed with 2-thiobarbituric acid by the Timyrbulatovum [11]. The concentration of protein was determined by the method of Lowry [20].

Data are expressed as mean.S.E.M. Differences among experimental groups were determined by ANOVA (analysis of variance), and the significance of between-group differences assessed by Student–Newman–Keul's multiple range test. Significance was defined at $P \leq 0.05$.

RESEARCH RESULTS AND THEIR DISCUSSION

After the experiment, final weight of control rats and rats that consumed the speciment of natural polyphenols complexes of grape wine increased by 36% compared with the beginning of the experiment (tabl. 1). In contrast to control body weight in groups of rats with diabetes, decreased slightly. At the same time the weight of rats with diabetes that consumed the speciment, increased by 36%.

In groups of rats with EDM this can be explained by the fact that diabetes is characterized by "overproduction" of urea. The last, due to osmotic diuresis, is excreted from the body with the amount of water and electrolyte K^+ and Na^+ ions necessary for it [17]. This process leads to dehydration, which further is enhanced. As a result of induction of release of free lipid acids from adipocytes and and subsequent conversion into ketone bodies that causes ketoacidosis [3].

The ketone bodies caused increase in osmotic diuresis and electrolyte loss [18], that locks a described device. Such changes in level of the water are unable not to affect not on the general metabolism. This can explain the significant differences of the weight in the group with diabetes compared to control one.

In groups of rats with EDM with consumption of speciment of polyphenols complexes the body weight almost resumed to control values. Received results are in line with the results obtained in experiments in which the speciment is used as a solution of red wine in water [3]. It has been shown that speciment has had corrective effect on blood glucose in control and in diabetic groups, as blood glucose concentration in diabetic groups was increasing throughout the experiment (tabl. 1).

Table 1

Body weight and blood glucose concentration in control and diabetic rats with or without polyphenol speciment consumption (M±m. n=5–7)

Rodent group	Blood glucose, mmol/l		Body weight, g	
	Initial §	Final	Initial §	Final
C	5.72±0.46	6.2±0.51	214±16.1	292±19.6
C+S	5.92±0.16	6.3±0.19	209±17.35	278±20
D	18.54±0.89**	26.82±2.23**	181±6.78	199±30**
D+S	20±0.29**	26.88±1.87**	188.3±6.41	257.5±10.47*, #

C – control; C+S – control+ speciment of polyphenols; D – diabetic; D+S – diabetic+ speciment of polyphenols. *, ** $P<0.05$ та < 0.01 against the control group. # $P<0.05$ against the control and diabetic group without polyphenol speciment consumption. § – 3rd day after induction of diabetes.

Analyzing the results, we can assume that the protective effect of polyphenols complexes is connected with the decrease in the level of ketone bodies at the stage of their utilization or deduction from the body by the system of the glomerul and tubules of the kidneys that is accompanied by stimulation of reabsorption of electrolytes and water from primary urine [3]. Establishing of the mechanisms of these phenomena, requires a detailed study in future.

It is known that DN is characterized by excessive formation of reactive oxygen and nitrogen (nitric oxide, superoxide anion, peroxynitrite, etc.) that cause multiple cytotoxic effects: activation of processes of lipid peroxidation, nitration and nitrosylation of proteins, DNA breaks, mitochondrial membrane depolarization and may induce necrosis and apoptosis [25, 28].

The intensity of free radical oxidation in the body depends on various factors, but prima-

rily are determined by the coordinated functioning of enzymes of antioxidant system of defence among which the main role belongs to superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase.

Under DM the activity of enzyme antioxidant system in rat kidney tissue changes. The activity of SOD in group with diabetes without speciment consumption decreased by 35.5% compared with control (fig. 1.). It can be associated with extremely high activity of the local renal renin-angiotensin system that is typical for this pathology. Pathogenic mechanisms of angiotensin II under conditions of diabetes are caused not only by its strong vasoconstractive effect, but also by proliferative, pro-oxidative activity. In the kidneys it causes the development of intraglomerular hypertension, contributes to sclerosilation and fibrosilation in kidney tissue [13]. Its impact on the reduction and growth of vascular smooth muscle it is carried through the generation of intracellular $O_2^{\cdot-}$, the main "liquidator" of which in living organisms is SOD. Overproduction of superoxide anion that is influenced by "overaffect" of angiotensin II and the disruption of the electron transport chain causes depletion of the protective system. Owing to this there is accumulation of superoxide-anion-radical which is subjected to rapid radical-radical interaction of NO with the formation of mediator of oxidative cell damage – peroxynitrite ($ONOO^-$). When peroxynitrite interacts with proteins, it nitrosylates them by tyrosine, altering their biological properties [27]. Besides peroxynitrite, the formation of products of protonation of the nitric oxide is reported which is particularly dangerous for the enzyme because it can modify amino acid residues of proteins, is reportwhich also can be manifested in the reduction of SOD activity [10]. The direct interaction NO with Cu^{2+} in SOD active center is possible leads to inhibition of its activity [10]. Not enzyme glycosylation of amino acid residues, part of which is contained in the active center of enzyme also affects the enzyme activity.

In the groupe of rats with DM with speciment consumption, the activity of SOD increases by 60% compared with a diabetic group without consumption of polyphenols (fig. 1). It is known that polyphenols have the protective properties and they are scavengers of ROS [3]. They can "pull" newly formed superoxide-anion-radicals and other ROS on themselves, which reduces the formation of dangerous substances such as peroxynitrite [3].

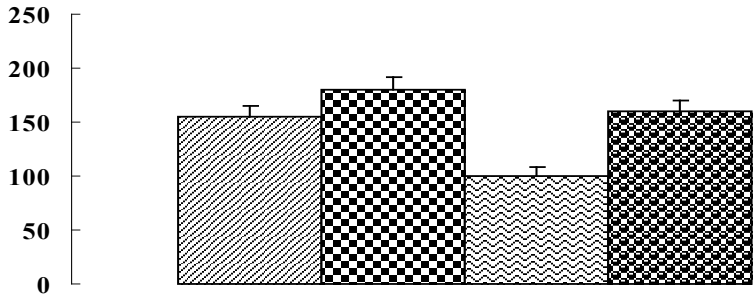

Fig. 1. The activity of superoxide dismutase in kidney: C – control; C+S – control+ speciment of polyphenols; D – diabetic; D+S – diabetic+ speciment of polyphenols. **P<0.01 compared with controls. ## P<0.01 compared with diabetic rats without speciment of polyphenols consumption.

We found that under DM the activity of CAT decreases by 69.7% compared with the control group (fig. 2). Reduction of the activity of this enzyme can be partly explained similarly to SOD.

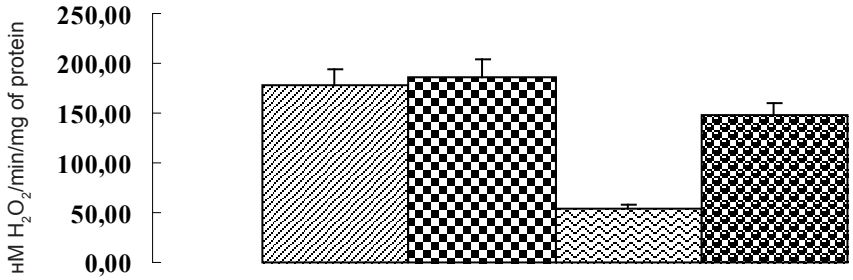

Fig. 2. The activity of catalase in kidney: C – control; C+S – control+ speciment of polyphenols; D – diabetic; D+S – diabetic+ speciment of polyphenols. **P<0.01 compared with controls. # P<0.05 compared with diabetic rats without speciment of polyphenols consumption.

Increase in NO production under diabetes has its definite impact on the CAT. Nitric oxide binds to ferrum-perforin complex of catalase, forming different forms of NO. The emergence of heme-NO complexes prevents binding of H_2O_2 in the active center of catalase and its scheduling. Nitrite ions can directly bind to the ferrum of enzyme heme, that can cause decreasing of the activity of the enzyme [10]. Under the consumption of speciment of polyphenols by the rats treated by DM the activity of CAT increased in 1.7 times (fig. 2) that is only by 17% below the activity of enzyme in control group. Usage of these antioxidants leads to the decrease in the flowing of free oxidation and as a result – increasing of the enzyme activity.

Glutathione system (GS) is especially important under oxidative-nitrosative stress (ONS). It provides effective protection of cells from the effects of ONS and therefore under its depletion serious consequences for the organism occured.GS eliminates ROS directly, or as the "second line of defense" after SOD and CAT, complements and completes the work of the «first line» and correctes it errors.

In particular, neutralization of hydrogen peroxide in addition to KAT carries GPO, whose affinity to H_2O_2 is significantly higher than in KAT [4]. In kidney tissue under DM the activity of GPO and GR is reduced by 19% and 30% respectively (fig. 3, *A*, *B*).

GPO activity depends on the content of reduced glutathione, which level of intracellular concentration supported by GR. Functioning of GR is determined by the level of reduced nicotinamide coenzymes. Under DM is energy depletion that leading to the energy substrates shortage which is directly impact proportional on the protective systems observed. There are no «energy coenzymes» – no effective protection. In group of rats with DM with speciment of polyphenols complexes consumption observed recovery of activity GPO and GR by 19% and 45% accordingly compared with group with DM without speciment consumption (fig. 3, *A*, *B*).

This increased activity of GPO and GR can be explained by improved energy state which is probably caused by the protective properties of natural polyphenol complexes. This issue requires more detailed studies. Intensification of free radical oxidation processes under affect of ROS leads to the increased lipid peroxidation (LPO), oxidative modification of proteins, degradation of nucleic acids, carbohydrates, etc. It causes structural and metabolic disturbances in cells [5]. The main marker of LPO is the presence of thiobarbituric acid -positive products. Under DM the level of this products is increased by 63.4% (fig. 4).

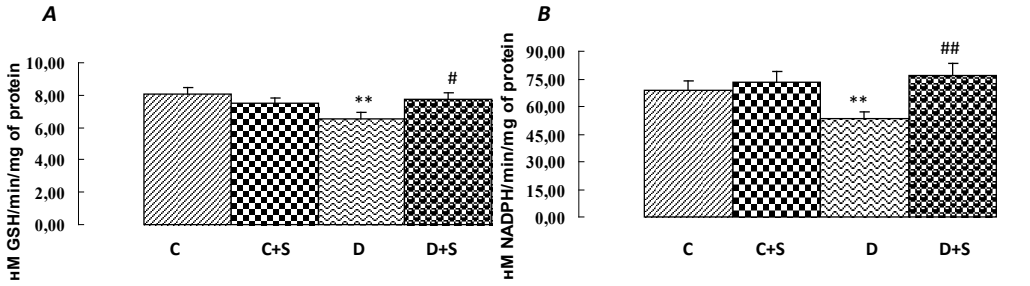

Fig. 3. The activity of antioxidant enzyme system in kidney: *A* – GPO, *B* – GR: C – control; C+S – control+ speciment of polyphenols; D – diabetic; D+S – diabetic+ speciment of polyphenols. **P<0.01 compared with controls. #, ## P<0.05 and 0.01 compared with diabetic rats without speciment of polyphenols consumption.

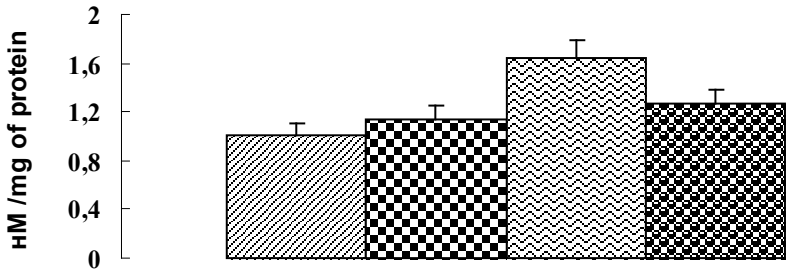

Fig. 4. TBK-positive content of LPO products: C – control; C+S – control+ speciment of polyphenols; D – diabetic; D+S – diabetic+ speciment of polyphenols. **P<0.01 compared with controls. # P<0.05 compared with diabetic rats without speciment of polyphenols consumption.

This can be explained by the fact that ROS oxidized lipids that leads to the accumulation of primary and secondary oxidation products [10]. Under speciment consumption by the group of rats treated by DM, this figure is reduced by 23% compared with the group without spaciment consumption. Intensification of LPO processes is due to the changes in the concentration of free radicals. The greater this concentration is the more intense processes of LPO. The natural polyphenols complexes being scavenger properties caused the reduction of free radicals and reduced the level of end products of LPO.

Thus, natural polyphenols complexes of grape wine have a significant antidiabetic effect at the level of the whole organism: they protect it from the dehydration, cause the increase in the activity of antioxidant enzyme system in kidney tissue. Thus, the activity of SOD, CAT, GPO and GR in groups with speciment consumption is increased by 60% and 170%, 19% and 45% respectively. TBK-positive content of LPO products is decreased by 23%.

A detailed study of the biochemical mechanisms of action of polyphenols of grape wine requires the following research, but certainly, these natural complexes can be used in the treatment of complications of diabetes and development of the new antidiabetic drugs.

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АНТИОКСИДАНТНИЙ ЕФЕКТ ПРИРОДНИХ ПОЛІФЕНОЛЬНИХ КОМПЛЕКСІВ ВИНОГРАДУ У ТКАНИНАХ НИРОК ЩУРІВ ЗІ СТРЕПТОЗОТОЦИН-ІНДУКОВАНИМ ЦУКРОВИМ ДІАБЕТОМ

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У роботі обговорюється протекторний ефект препарату природних поліфенольних комплексів винограду у тканинах нирок білих щурів за умов цукрового діабету 1-го типу, що відображається в активації ферментативної антиоксидантної системи організму та зниженні патогенної дії активних форм кисню, які лежать в основі механізмів різних діабетичних ускладнень, зокрема нефропатій.

Ключові слова: цукровий діабет, поліфенольні комплекси, діабетична нефропатія, оксидативний стрес, антиоксидантний захист.

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ПРОТЕКТОРНЫЙ АНТИОКСИДАНТНЫЙ ЭФФЕКТ ПРИРОДНЫХ ПОЛИФЕНОЛЬНИХ КОМПЛЕКСОВ ВИНОГРАДА В ПОЧКАХ КРЫС СО СТРЕПТОЗОТОЦИН-ИНДУЦИРОВАННЫМ САХАРНЫМ ДИАБЕТОМ

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В работе обсуждается возможный протекторный эффект препарата природных полифенольных комплексов винограда в почках белых крыс в условиях сахарного диабета 1-го типа, что отражается в активации ферментативной антиоксидантной системы организма и снижении патогенного действия активных форм кислорода, лежащих в основе различного рода механизмов диабетических поражений, в частности нефропатий.

Ключевые слова: сахарный диабет, полифенольные комплексы, диабетическая нефропатия, оксидативный стресс, антиоксидантная защита.