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EFFECTS OF AGMATINE AND RED WINE CONCENTRATE, ENRICHED WITH POLYPHENOLIC COMPOUNDS, ON L-ARGININE / NITROGEN OXIDE SYSTEM IN THE BRAIN OF RATS WITH EXPERIMENTAL DIABETES MELLITUS

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Background. Diabetes mellitus is a chronic endocrine metabolic disease with absolute or relative insufficiency of insulin, accompanied by impaired metabolism. Endogenous bioamine agmatine may become a basis of new antidiabetic drugs, as it is capable to induce the release of some peptide hormones, in particular insulin, and can regulate NO synthesis. Natural polyphenols are potential multifunctional agents that also can reduce the risk of diabetes and diabetic complications. The aim of the study was to evaluate the effect of agmatine and red wine concentrate, enriched with polyphenolic compounds, on NO-synthase activity and the content of NO stable metabolites under experimental diabetes mellitus.

Materials and Methods. The experiments were conducted on white Wistar male rats. Diabetes was induced by intra-abdominal injection of streptozotocin. From the 14th day after the induction of diabetes, agmatine was injected intramuscularly or red wine concentrate, enriched with polyphenolic compounds was administrated orally to animals for 14 days. Rats were decapitated under ether anesthesia on the 28th day of the experiment. In the brain of rats, the activity of constitutive (Ca^{2+}-dependent) and inducible (Ca^{2+}-independent) isoforms of NO-synthase and the content of nitrite and nitrate anions were determined.

Results and Discussion. The activities of constitutive and inducible isoforms of NO-synthase were increased in the brain of diabetic rats. The administration of both agmatine and red wine concentrate, enriched with polyphenolic compounds, caused the reduction of the activities of NO-synthase isoforms. In the case of diabetes, the administration of agmatine contributes to the increase of nitrite and nitrate content in brain cells

compared to diabetes. The administration of red wine concentrate, enriched with polyphenolic compounds, also promotes nitrite levels but does not affect the nitrate level.

Conclusion. We found that the red wine concentrate, enriched with polyphenolic compounds, has a stronger effect on the activity of Ca^{2+}-dependent and Ca^{2+}-independent isoforms of NO-synthase, as well as the content of nitrites and nitrates in brain of rats with experimental diabetes mellitus, compared to the effect of agmatine.

Keywords: agmatine, red wine concentrate, polyphenolic compounds, diabetes mellitus, NO-synthase, nitrite anions, nitrate anions

INTRODUCTION

Diabetes mellitus is a chronic endocrine metabolic disease caused by the action of endogenous and exogenous factors, with absolute or relative insufficiency of insulin, accompanied by impaired metabolism [10]. Under the pathology, hyperglycemia causes the generation of Reactive Oxygen and Nitrogen Species, which initiate lipid peroxidation and modification of proteins [17]. The posttranslational modification of intracellular proteins contribute to changes in signal transduction, loss of enzymes activity, and reduction of biosynthetic processes. Although neurons are insulin-independent cells, changes occur in the nervous system in diabetes.The reason for diabetic neuropathy development is the accumulation in the nervous tissue of glucose, fructose, and sorbitol – alcohol, which is created due to the activation of the polyol pathway of glucose metabolism [22].

The problem of finding new low-toxic antidiabetic drugs that have contributed to the development of oxidative-nitrative stress and previous damage to the nervous system is relevant.

Agmatine, 4-aminobutyl guanidine, is an endogenous amine, synthesized from L-arginine in a reaction catalyzed by arginine decarboxylase. Agmatine is synthesized in different tissues including the central nervous system of mammals. In the brain, agmatine plays a role of a neurotransmitter/neuromodulator as it binds to a2-adrenergic and imidazoline (I1) receptors. In addition, agmatine antagonizes N-methyl-D aspartate receptors (NMDAR), inhibits all isoforms of NO synthase, and modulates polyamine metabolism [6, 8, 18]. Agmatine possesses mild hypoglycemic effects, inhibits advanced glycation end product (AGE) formation [19], influences protein ADP-ribosylation and hence signaling pathways [21]. These data determine the possibility of using agmatine to correct metabolic disorders in the brain in diabetes.

Other substances that can potentially be used to suppress pathological changes in the central nervous system are wine polyphenols. In recent years, there has been growing evidence that plant polyphenols, due to their biological properties, can be used as unique dietary supplements that should be used in diabetes [3]. Plant polyphenols reduce the risk of developing diabetes and diabetic complications [20, 24]. Polyphenolic complexes of grapes are characterized by enzyme-modulating, chelating, and scavenger effects, which are especially important in diabetes because hyperglycemia causes the formation of free radicals [10].

The aim of the study was to evaluate the effect of agmatine and red wine concentrate, enriched with polyphenolic compounds, on NO-synthase activity, nitrite and nitrate content under experimental diabetes conditions.

MATERIALS AND METHODS

The study was performed on white outbred male Wistar rats of 150–200 g weight. The animals were kept in standard vivarium conditions with free access to food and water. The experiments were carried out in accordance with the national General Ethical Principles for Animal Experiments approved by the First National Congress on Bioethics (Kyiv, Ukraine, 2001), which are agreed with the guidelines of Directive 2010/63/EU of the European Parliament on the protection of animals used for scientific purposes and the Law of Ukraine "On Protection of Animals from Cruelty" of February 26, 2006, and also approved by the Bioethics Committee of Ivan Franko National University of Lviv, Ukraine (Protocol No. 21-05-2021 від May 28, 2021).

Animals were divided into groups: 1 – control, 2 – control animals injected with agmatine, 3 – control animals injected with polyphenolic compounds (PC) concentrate, 4 – animals with experimental diabetes mellitus, 5 – animals with diabetes, which were administered agmatine, 6 – animals with diabetes, which were injected with PC concentrate.

Experimental diabetes was induced by intraperitoneal injection of streptozotocin (Sigma, USA) dissolved in 10 mM citrate buffer (pH 5.5) at a dose of 60 mg per 1 kg of body weight. The development of diabetes was monitored by blood glucose measurement, which was determined after 5 days of administration of streptozotocin. In the experiment were used animals with a glucose level greater than 14 mmol/L. From the 14th day after the induction of diabetes, the animals from the 2nd and 5th group were injected intramuscularly with agmatine (Sigma, USA) at a concentration of 20 mg per 1 kg of body weight for 14 days. To animals from the 3rd and 6th group was orally administrated PC concentrate by tube. PC concentrate was obtained from dry red grape wine by evaporation on a rotary evaporator Laborota 4001 (Germany) at a temperature of 40 °C. Subsequent stabilization with ethanol (up to a final concentration of 30%) and biogenic surfactants (up to a final concentration of 3%) [26]. PC concentrate immediately before administration was diluted in water to a final volume of 1 ml, and the amount of administrated PC concentrate was calculated according to the weight of the animal to achieve a dose of 45 mg of polyphenolic compounds on 1 kg of body weight.

Rats from all experimental groups were decapitated under ether anesthesia on day 15 of the experiment. Brain extraction was performed, and the samples were immediately frozen at -70 °C. Homogenization of frozen brain tissue was performed at an ice bath at 4 °C using a manual Potter–Ellweem homogenizer in the presence of hypotonic 50 mm Na–K phosphate buffer (pH 7.4) at the rate of 50 mg of brain tissue in 100 μL of buffer. The studied parameters were determined in the supernatant obtained after centrifugation of lysates for 5 minutes at 10,000 rpm.

Protein concentration was determined according to the conventional Lowry method [13].

The total activity of NO synthase and the activity of Ca^{2+}-independent NO synthase were determined by the difference in the formation of nitrites with the minimum number of cofactors to approximate the activity of the enzyme to the initial level of activity in the test samples [5]. NOS activity in the sample was expressed in nmol of NO_2^- for 1 min per 1 μg of protein.

The content of nitrite anions and nitrate anions was measured using Griess reagent [15]. To determine the content of nitrate anions, VCl_3 was added in addition to Griess reagent.

Statistical analysis of the results obtained was carried out using Microsoft Excel 2013. The calculation of basic statistical parameters was performed by direct quantitative data obtained from the study (arithmetic mean – M, the standard deviation of the arithmetic mean – SD).

To assess the reliability of the difference between statistical characteristics of the two alternative data sets, we performed Student's *t*-test. The difference was considered significant under $p \geq 0.95$ (the level of significance $P < 0.05$).

RESULTS AND DISCUSSION

There are two pathways of L-arginine metabolism in the body: non-oxidative conversion to urea and ornithine and the oxidative pathway catalyzed by NO-synthase. Enzymes of the NO-synthase family produce Nitrogen Oxide (II), using an Oxygen molecule. Under pathological conditions, the reduction of the Oxygen molecule with the participation of NO-synthases is associated with the generation of superoxide anion. This significantly increases oxidative stress [9].

In the last few years, several NO-synthase inhibitors have been developed. Most of these drugs are analogs of L-arginine. The relevance of the use of agmatine as an inhibitor of NO-synthase is that this amine occurs naturally in mammalian systems [9]. Agmatine duces the release of certain peptide hormones, in particular insulin, so it possesses a hypoglycemic effect. Today, agmatine is studied as a substance that inhibits neurodegeneration and protects the liver. Agmatine binds free radicals, inhibiting the further development of oxidative stress [1], protecting against the oxidation of sulfhydryl groups, and reducing the level of hydrogen peroxide [2].

We have shown that under experimental diabetes mellitus, the activity of constitutive isoforms of NO-synthase increased by 7.6 times in the brain of rats compared to the control (**Fig. 1**). In the brain of animals with diabetes, agmatine injections caused a decrease in NO-synthase activity by 2.5 times, but this index was still higher than control values (**Fig. 1**).

In the case of injection of agmatine to animals of the control group, the activity of Ca^{2+}-dependent isoforms in the brain is 5.9 times higher than in the control. Probably, agmatine causes an increase in the concentration of Ca^{2+} in nervous tissue cells due to changes in its release from intracellular depots. It is known that agmatine causes a decrease in calcium concentration by activating the SERCA pump (sarco (endo) plasmic Ca^{2+} ATPase) in endothelial cells and, in addition, can activate ARC channels (arachidonic acid-regulated Ca^{2+}-permeable channels), and thus increases the release of Ca^{2+} from intracellular depots in the cytosol [14].

In recent years, it has become increasingly clear that plant food polyphenols, due to their biological activity, can be unique dietary supplements and adjuvants in the treatment of diabetes [3]. The red wine polyphenol complex includes potential multifunctional agents that reduce the risk of developing diabetes and diabetic complications [20].

The administration of PC concentrate to animals with diabetes caused a decrease in the activity of Ca^{2+}-dependent NO-synthase by 6 times compared to diabetes (**Fig. 1**).

The activity of inducible NO-synthase increased in the brain of rats with diabetes by 4.2 times (**Fig. 2**) compared to the control. In the case of the injection of agmatine to animals with the pathology, a 2.4-fold decrease of the index was obsedved compared to diabetes. The detected changes may be caused by the accumulation of non-enzymatic glycation products under conditions of hyperglycemia, which stimulates the formation of

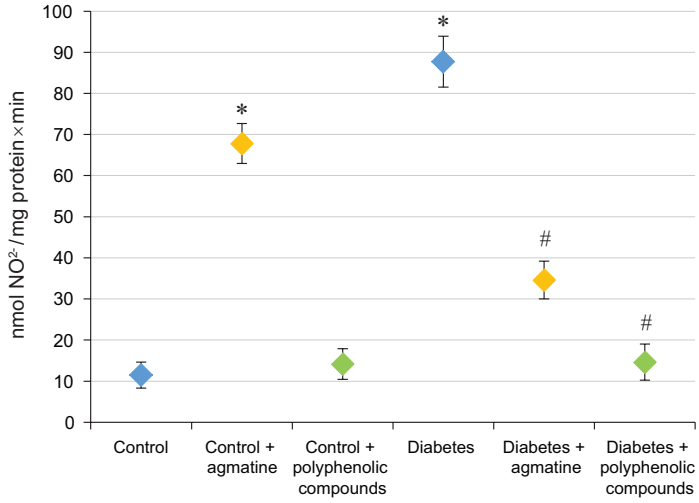

Fig. 1. The activity of constitutive isoforms of NO-synthase in the brain of rats under conditions of diabetes mellitus, andon the background of the injection of agmatineor administration of polyphenolic compounds concentrate. * – the difference is significant compared to control (p≥ 0.95); # – the difference is significant compared to diabetes (p≥ 0.95)

Рис. 1. Активність конститутивних ізоформ NO-синтази у головному мозку щурів за умов цукрового діабету й на тлі введення агматину, або введення концентрату природного поліфенольного комплексу з червоного виноградного вина. * – різниця достовірна порівняно з контролем (p≥ 0,95); # – різниця достовірна порівняно з діабетом (p≥ 0,95)

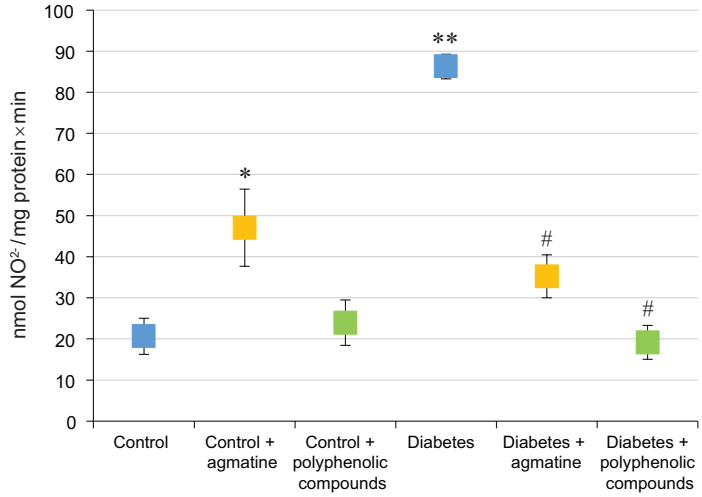

Fig. 2. Activity of inducible isoform of NO-synthase in the brain of rats under conditions of diabetes mellitus, and on the background of the injection of agmatine or administration of polyphenolic compounds concentrate. * – the difference is significant compared to control (p≥ 0.95); ** – the difference is significant compared to control (p≥ 0.99); # – the difference is significant compared to diabetes (p≥ 0.95)

Рис. 2. Активність індуцибельної ізоформи NO-синтази у головному мозку щурів за умов цукрового діабету й на тлі введення агматину, або введення концентрату природного поліфенольного комплексу з червоного виноградного вина. * – різниця достовірна порівняно з контролем (p≥ 0,95); ** – різниця достовірна порівняно з контролем (p≥ 0,99); # – різниця достовірна порівняно з діабетом (p≥ 0,95)

proinflammatory cytokines that induce the expression of the inducible NO-synthase gene and, consequently, the excessive formation of nitrogen oxide [7].

Under the administration of PC concentrate, we observed a 4.5-fold reduction in the activity of inducible NO-synthase in rats with diabetes compared to the pathology (**Fig. 2**). Our results conform with the literature, which states that polyphenolic compounds have excellent effects on the activity of various isoforms of the enzyme: inhibit inducible NO-synthase, and, on the contrary, increase the activity of Ca^{2+}-dependent NO-synthase [25].

It is known that some parts of NO can be inversely converted into less active substances – nitrites and nitrates ions. These ions are the main mechanism for reducing NO toxic effects. In the brains of diabetic animals, the level of nitrates was increased by 1.2 times (**Fig. 4**), while the level of nitrites did not change (**Fig. 3**). The obtained data are reflecting the changes in NO-synthase activity.

After the injection of agmatine to animals with diabetes, the nitrate and the nitrite contents increase by 1.7 times (**Fig. 4**, **Fig. 3**), compared to pathology.

A 2.2-fold increase in nitrite levels was found in the brains of rats with diabetes mellitus when PC concentrate was administered compared to data without concentrate administration (**Fig. 3**). The level of nitrates did not change significantly in any of the studied groups under the administration of PC concentrate (**Fig. 4**).

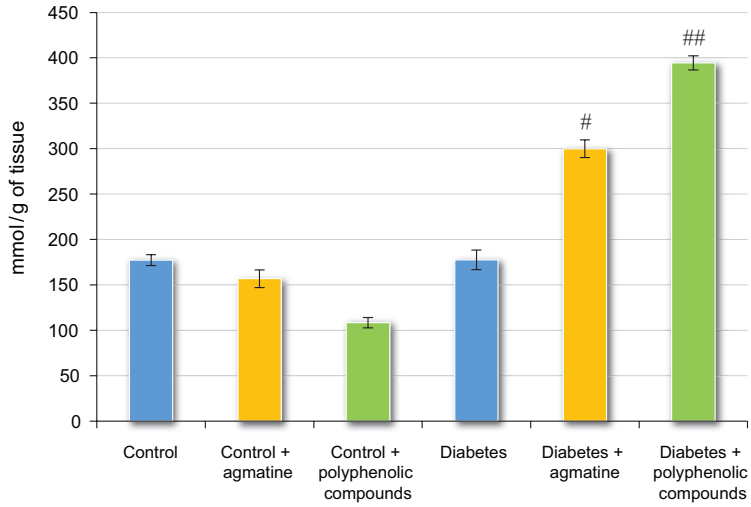

Fig. 3. The content of nitrites in the brain of rats under conditions of experimental diabetes mellitus, without and with the introduction of agmatine (orange columns), or administration of polyphenolic compounds concentrate (green columns). # – the difference is significant compared to diabetes (p≥ 0.95); ## – the difference is significant compared to diabetes (p≥ 0.99)

Рис. 3. Вміст нітритів у головному мозку щурів за умов експериментального цукрового діабету, без та за введення агматину (оранжеві стовпчики), або за введення концентрату природного поліфенольного комплексу з червоного виноградного вина (зелені стовпчики). # – різниця достовірна порівняно з діабетом (p≥ 0,95); ## – різниця достовірна порівняно з діабетом (p≥ 0,99)

Excess NO formation reflected in the accumulation of nitrites and nitrates, with a decrease in NO-synthase activity can be caused by two mechanisms. Firstly, by activating of enzyme-independent pathways of NO production. Secondly, NO is released from its depots, which were formed due to S-nitrosylation of proteins with subsequent oxidation of NO to NO_2^- and NO_3^-. Polyphenolic compounds of grape wine have an ability

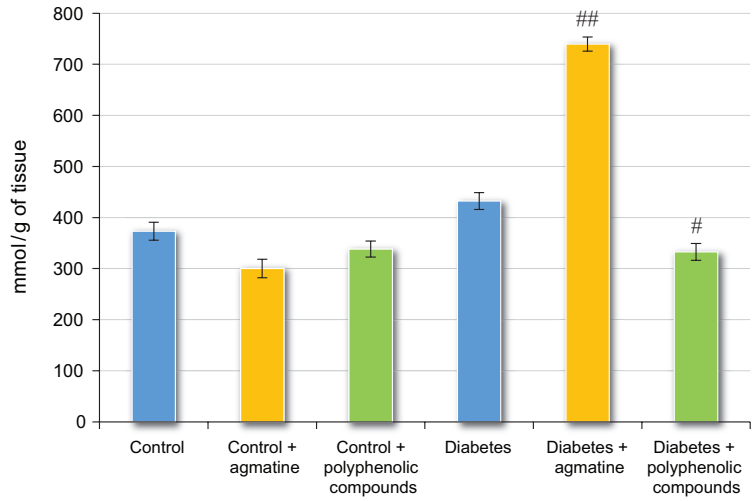

Fig. 4. The content of nitrates in the brain of rats under conditions of experimental diabetes mellitus, without and with the introduction of agmatine (orange columns), or administration of PC concentrate(green columns). # – the difference is significant compared to diabetes (p≥ 0.95); ## – the difference is significant compared to diabetes (p≥ 0.99)

Рис. 4. Вміст нітратів у головному мозку щурів за умов експериментального цукрового діабету, без та за введення агматину (оранжеві стовпчики), або за введення концентрату природного поліфенольного комплексу з червоного виноградного вина (зелені стовпчики). # – різниця достовірна порівняно з діабетом (p≥ 0,95); ## – різниця достовірна порівняно з діабетом (p≥ 0,99)

to capture and neutralize NO and its metabolites [11, 16]. But it is considered that the key pathway through which polyphenols affect the level of NO and its stable metabolites in diabetic neuropathy is the influence on the activity of NO-synthase. Polyphenols alter the kinase signaling for instance PI3-kinase/Akt pathway and intracellular Ca^{2+}. It leads to NO-synthase constitutive isoforms phosphorylation which ultimately results in NO production [12, 23]. At the same time, polyphenols may downregulate transcription factor NF-κB [27, 28], which results in inhibition of the expression of gene encoding inducible isoform of NOS [3] and a decrease in NO level.

CONCLUSION

Agmatine and PC concentrate modulated the activity of both constitutive and inducible isoforms of NO-synthase in the central nervous system of rats with experimental diabetes mellitus. In addition, the content of NO stable metabolites under the conditions of diabetes increased after the introduction of agmatine and red wine concentrate, enriched with polyphenolic compounds.

Thus, we found that the red wine concentrate, enriched with polyphenolic compounds, possessed a stronger effect on the activity of constitutive and inducible isoforms of NO synthase, as well as the content of nitrites and nitrates. Red wine concentrate did not affect NO-synthase in control, while agmatine did, suggesting that agmatine is a less effective neuroprotector in diabetic neuropathy.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Human Rights: This article does not contain any studies with human subjects performed by any of the authors.

Animal Studies: All institutional, national and institutional guidelines for the care and use of laboratory animals were followed.

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ПОРІВНЯННЯ ЕФЕКТУ АГМАТИНУ ТА КОНЦЕНТРАТУ ЧЕРВОНОГО ВИНОГРАДНОГО ВИНА, ЗБАГАЧЕНОГО ПРИРОДНИМ ПОЛІФЕНОЛЬНИМ КОМПЛЕКСОМ, НА СИСТЕМУ L-АРГІНІН / ОКСИД НІТРОГЕНУ В ГОЛОВНОМУ МОЗКУ ЩУРІВ ЗА ЕКСПЕРИМЕНТАЛЬНОГО ЦУКРОВОГО ДІАБЕТУ

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Вступ. Цукровий діабет – це хронічне ендокринне метаболічне захворювання з абсолютною або відносною недостатністю інсуліну, що супроводжується порушенням обміну речовин. Ендогенний біоамін агматин може бути використаний як основа нових протидіабетичних препаратів, оскільки він зумовлює вивільнення деяких пептидних гормонів (зокрема, інсулін), а також може конкурентно інгібувати NO-синтазу й, отже, регулювати утворення NO. Природні поліфеноли – потенційні багатофункціональні агенти, що знижують ризик діабету й ускладнень діабету. Метою дослідження було оцінити вплив агматину та концентрату червоного виноградного вина, збагаченого природним поліфенольним комплексом (концентрат поліфенольного комплексу), на активність NO-синтази, вміст стабільних метаболітів оксиду нітрогену (II) за експериментального цукрового діабету.

Матеріали та методи. Дослідження проводили на білих безпородних щурах-самцях лінії Wistar. Цукровий діабет індукували одноразовим внутрішньоочеревинним введенням стрептозотоцину. З 14 дня після індукції діабету тваринам упродовж 14 днів внутрішньом'язово вводили агматин або перорально вводили концентрат поліфенольного комплексу. Тварин із усіх дослідних груп декапітували під ефірним наркозом на 28-й день експерименту, зразки негайно заморожували за -70 °C. У мозку тварин визначали активність конститутивних (Ca^{2+}-залежних) та індуцибельної (Ca^{2+}-незалежної) ізоформ NO-синтази, вміст нітрит-аніонів і нітрат-аніонів.

Результати. Активність конститутивних та індуцибельної ізоформ NO-синтази підвищувалася в мозку щурів з цукровим діабетом порівняно з контролем. Як введення агматину, так і введення концентрату червоного вина, збагаченого природним поліфенольним комплексом, спричиняло зниження активності NO-синтази. За цукрового діабету введення агматину сприяло збільшенню вмісту нітритів і нітратів у клітинах мозку порівняно з діабетом. Введення концентрату поліфенольного комплексому також сприяє підвищенню рівня нітритів, але не впливає на рівень нітратів.

Висновки. Отже, ми довели, що концентрат червоного виноградного вина, збагаченого природним поліфенольним комплексом, чинить сильніший ефект на активність Ca^{2+}-залежних і Ca^{2+}-незалежних ізоформ NO-синтази у головному мозку щурів з експериментальним цукровим діабетом, порівняно з ефектом агматину.

Ключові слова: агматин, концентрат червоного вина, поліфенольні сполуки, цукровий діабет, NO-синтаза, нітрит-аніони, нітрат-аніони

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