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# EFFECT OF POLYPHENOL COMPOUNDS ON THE AORTA STATE IN MALE AND FEMALE RATS UNDER CONDITIONS OF HYPERHOMOCYSTEINAEMIA

***Abstract*** *Hyperhomocysteinemia is associated with the development of oxidative stress in the heart and vessels. The ability of different bioflavonoids to correct the processes of free radical oxidation in the aorta in male and female rats under this pathology remains unknown. Therefore, the objective of the work was to study the effect of genistein and quercetin bioflavonoids on the development of endothelial dysfunction and changes of the pro-antioxidant system in the aorta of different gender rats induced by hyperhomocysteinemia. Administration of genistein under conditions of hyperhomocysteinemia was found to restrain the development of endothelial dysfunction, reduce superoxide dismutase activity, prevent hyperactivity of NADPH-oxidase and the processes of free radical lipid and protein oxidation in the aorta of male and female rats. Under these conditions the effect of quercetin on the above processes was considerable lower than that of genistein.*

***Key words:*** *hyperhomocysteinemia, oxidative stress, aorta, genistein, quercetin, gender.*

**Introduction.** Hyperhomocysteinemia (HHC) is a common independent risk factor of cardio-vascular pathology [1]. One of the molecular mechanisms of endotheliotoxic action of homocystein high doses is development of oxidative stress [1]. Under conditions of hyperhomocysteinemia pro-antioxidant imbalance develops in the aorta, the processes of free radical lipid and protein oxidation intensify which is associated with the development of endothelial dysfunction. Nowadays with the purpose to correct the functional state of vessels polyphenol compounds are widely used (genistein, quercetin etc.) which manifest antioxidant and anti-inflammatory properties [2, 3]. At the same time genistein is found to demonstrate hyperhomocysteinemic action under conditions of experimental methionine HHC [4]. Although, the ability of bioflavonoids to correct the processes of lipid and protein peroxidation in the aorta in male and female rats under HHC conditions remains unknown.

**Objective:** to study the effect of genistein and quercetin bioflavonoids on the development of endothelial dysfunction and changes of the pro-antioxidant system in the aorta of male and female rats induced by hyperhomocysteinemia.

**Materials and methods.** The experiments were conducted on 80 albino laboratory rats of both genders with the body weight of 220-280 g. The animals were kept under standard conditions with natural light regimen day/night, water and food were supplied *ad libitum*. The animals were fed on semisynthetic starch-casein diet with a balanced content of all the macro- and micronutrients. The study was conducted according to general ethical principles of experiments on animals due to the First National Congress of Ukraine on Bioethics (Kyiv, 2001) and European Convention on Protection of Vertebrate Animals Used for Experimental and Scientific Purposes (Strasburg, 1986).

Hyperhomocysteinemia model was designed by means of introduction of thiolactone D, L-homocysteine (Sigma, USA) intragastrically in the dose of 100 mg/kg of the body weight on 1% starch solution once a day during 28 days [5]. The two groups of animals (10 males and females in each) in addition to thiolactone homocysteine received genistein (2,5 mg/kg of the body weight intragastrically on 1% starch solution once a day) [4], and a part of them (10 males and females) quercetin (25 mg/kg of the body weight intragastrically on 1% starch solution once a day) during 28 days. The animals were killed by decapitation under propofol narcosis [6].

Activity of NADPH-oxidase (КФ 1.6.3.1), superoxide dismutase (КФ 1.15.1.1), the content of Malone dialdehyde (MDA) and carbonyl protein groups (CPG) were detected by means of spectrophotometric method [7]. The content of homocysteine in the blood serum was determined

by means of the set «Homocysteine EIA» (Axis-Shield, England). The content of vascular cell adhesive molecule-1(sVCAM-1) in the blood serum was detected by means of immune enzymatic method with the kit "sVCAM-1 ELISA KIT" (Diaclone, France) according to the instructions supplied by the producer. The results were statistically processed by means of the program SPSS Statistica 17.0. Difference reliability between the indices was assessed by the parametric Student t-criterion (in case of normal distribution) and non-parametric Mann-Whitney U-criterion (in case of contradiction to normal distribution). The data were considered reliable with p<0,05.

**Results and discussion.** Administration of thiolactone homocysteine is associated with 2,1 and 1,8 increase of homocysteine content in males and females respectively (p<0,05), as compared to the control. The use of genistein under these conditions demonstrates hyperhomocysteinemic effect: the level of homocysteine in malea and females was 50,3 and 37,1% down respectively (p<0,05), as compared to the "HHC" group. On the other hand, administration of quercetin does not effect the level of homocysteine in the blood.

Applied pharmacotherapy restrained imbalance of pro-antioxidant enzymes in the aorta of rats under HHC conditions with different efficacy (Table 1). Thus, 28-day introduction of thiolactone homocysteine causes reliable increase of NADPH-oxidase activity in the aorta of males to 46,2% (p<0,05), and in females – to 31,6% (p<0,05) and decrease of superoxide dismutase activity on 34,1 and 20,7% (p<0,05) in males and females respectively as compared to the control indices. At the same time, in the "HHC + genistein" group activity of the pro-oxidative enzyme NADPH-oxidase in the aorta appeared to be 26,8% less (p<0,05) in males and 17,8% less - in females (p<0,05), as compared to the group of untreated animals. At the same time, activity of antioxidant enzyme superoxide dismutase in the aorta was 47,6% up in males (p<0,05), and 22,8% up – in females (p<0,05), as compared to the group of untreated animals. Administration of quercetin less than genistein contradicts the development of imbalance between pro- and antioxidant enzymes in the aorta: NADPH-oxidase activity appeared to be 17,2% less in males (p<0,05) and19,0% in females (p<0,05), while superoxide dismutase activity was 24,7% more in males (p<0,05), and 20,9% more in females (p<0,05), as compared to the group of untreated animals.

Pharmacotherapy restrained the development of HHC-induced oxidative stress in the aorta, although it differed considerably by its efficacy depending on the drug of choice (Table 2). In animals with HHC a reliable increase of MDA and CPG was found in the aorta: 83,1 and 99,7% up in males (p<0,05), and 60,5 and 76,4% up in females (p<0,05) respectively as compared to the control. Genistein anticipates quercetin by its antioxidant action in males and females. Introduction of genistein was associated with a reduced activity of lipid peroxidation and protein oxidative destruction in the aorta under HHC conditions: the content of MDA and CPG in males became 43,6 and 45,2% less (p<0,05), and in females 33,6 and 35,5% less (p<0,05), as compared to the untreated animals. Under conditions of genistein administra-

**Table 1**

**Genistein and quercetin effect on the activity of pro- and antioxidant enzymes in the aorta of rats of both genders under HHC conditions (M±m, n=10)**

| № | Groups of animals | Gender | NADPH-oxidase, nmol/min·mg protein | Superoxide dismutase, s.u./mg protein |
|---|---|---|---|---|
| 1 | Control | Males | 0,85±0,04 | 2,25±0,09 |
| 2 | | Females | 0,61±0,03 | 2,71±0,11 |
| 3 | HHC | Males | 1,24±0,08* | 1,48±0,04* |
| 4 | | Females | 0,80±0,04* | 2,15±0,09* |
| 5 | HHC+ Genistein | Males | 0,91±0,05# | 2,19±0,07# |
| 6 | | Females | 0,66±0,02# | 2,64±0,08# |
| 7 | HHC+ quercetin | Males | 1,03±0,04*# | 1,85±0,05*# |
| 8 | | Females | 0,65±0,03# | 2,60±0,06# |

*Notes: 1. * - statistically reliable difference (p<0,05) relatively to the appropriate control group;*
*2. # - statistically reliable difference (p<0,05) relatively to the appropriate group with HHC.*

**Table 2**

**Genistein and quercetin effect on the content of products of lipid and protein peroxidation in the aorta of rats of both genders under HHC conditions (M±m, n=10)**

| № | Groups of animals | Gender | MDA, mcmol/g tissue | CPG, nmol/ml protein |
|---|---|---|---|---|
| 1 | Control | Males | 6,45±0,21 | 0,74±0,03 |
| 2 | | Females | 5,08±0,14 | 0,51±0,02 |
| 3 | HHC | Males | 11,8±0,34* | 1,48±0,06* |
| 4 | | Females | 8,15±0,22* | 0,90±0,03* |
| 5 | HHC+genistein | Males | 6,66±0,23# | 0,81±0,05# |
| 6 | | Females | 5,41±0,17# | 0,58±0,04# |
| 7 | HHC+quercetin | Males | 7,30±0,19*# | 1,05±0,08*# |
| 8 | | Females | 5,31±0,13# | 0,66±0,07# |

*Notes: 1. * - statistically reliable difference (p<0,05) relatively to the appropriate control group;*
*2. # - statistically reliable difference (p<0,05) relatively to the appropriate group with HHC.*

tion the indices of MDA and CPG were close to those of the control group. Administration of quercetin produces less pronounced antioxidant action in males and females under conditions of modeled pathology: the content of MDA and CPG in males was 38,2 and 29,0% down respectively (p<0,05), and in females - 34,8 and 26,6% down (p<0,05), as compared to untreated animals. Under these conditions the values of MDA and CPG in males are reliably higher than those in the control group of animals.

Administration of genistein and quercetin is associated with endotheliotropic action under HHC conditions, although their effect differs considerable in males and females (Figure). On the 28$^{th}$ day of administration of thiolactone homocystein the content of sVCAM-1 in males becomes 50,3% higher (p<0,05), and in females - 35,6% higher (p<0,05). At the same time, in "HHC+genistein" group sVCAM-1 content in the blood of males is reliable less on 32,2% (p<0,05), and in females – on 23,0% (p<0,05), as compared to untreated animals. Under this pathology quercetin demonstrated reliably less endothelial protection action. In "HHC+quercetin" group sVCAM-1 in males was 20,7% less (p<0,05), and in females – 19,7% less (p<0,05), as compared to untreated animals. Administration of quercetin in male rats does not correspond to those values of sVCAM-1 in the control group. Therefore, introduced pharmacotherapy corrected the processes of free radical oxidation and disorders of functional vascular state induced by HHC in rats of both genders with different

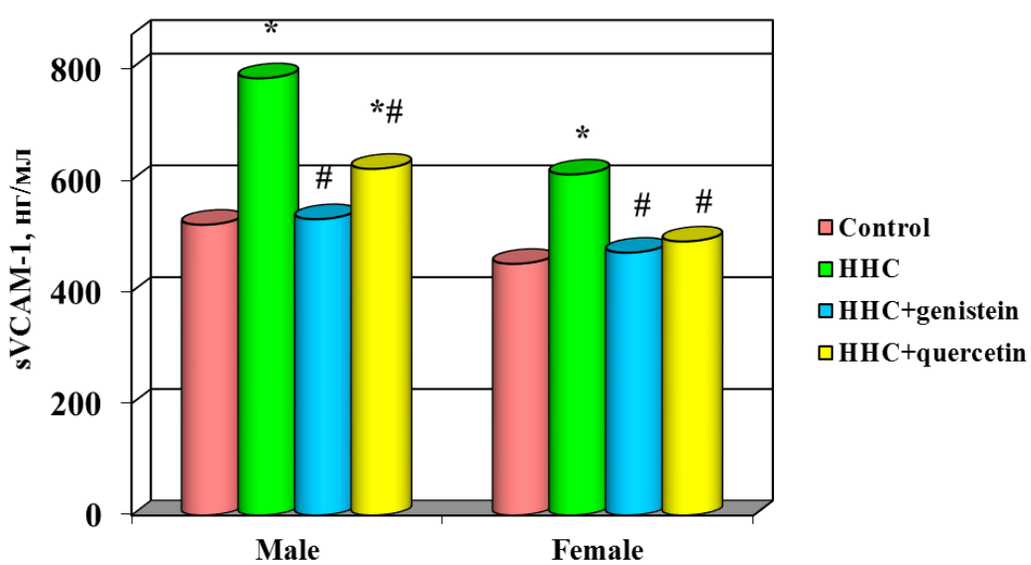


*Figure – Effect of genistein and quercetin on the content of VCAM-1 in the blood of rats of both genders under HHC conditions. Notes: * - statistically reliable difference (p<0,05) concerning the appropriate control group; # - statistically reliable difference (p<0,05) concerning the group with HHC.*

efficacy. Administration of genistein prevents HHC-induced decrease of the activity of superoxide dismutase, hyperactivation of NADPH-oxidase, processes of lipid peroxidation and protein oxidation modification in the aorta which is associated with restoration of the endothelial functional state. On the contrary, quercetin efficacy under these conditions was not so high as that of genistein.

High antioxidant activity of polyphenol compounds of quercetin and genistein is proved by literary data [2, 3, 6]. A question arises concernignpossible causes of higher antioxidant activity of genistein as compared to quercetin. Among polyphenols studied only genistein demonstrates its hyperhomocysteinemic activity. At the same time, high concentrations of homocysteine cause the developemnt of oxidative stress [1]. Therefore, ability of genistein to reduce the level of homocysteine in the blood is one of the factors of more pronounced antioxidant action of this bioflavonoid.

**Conclusions.** 1. Administration of the examined bioflavonoids restrains HHC-induced activation of NADPH-oxidase activation, processes of free radical oxidation of lipids and proteins, prevents reduced activity of superoxide dismutase in the aorta of male and female rats. Under these conditions genistein efficacy is higher than that of quercetin.

2. Under HHC conditions genistein demonstrates more pronounced endothelial protective action in males and females than quercetin.

**Prospects of further studies.** Investigations in this direction will enable to elaborate effective approaches concerning the correction of pathological changes in the vessels associated with metabolic disorders of sulfur-containing amino acids.

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