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Experimental substantiation of the use of quercetin for the correction of functional disorders in diabetes mellitus

Summary

The diabetes mellitus is an acute medical and social problem demanding the search of different methods of carbohydrate metabolism correction. The literature data during the last years indicate that parallel with medical drugs the protective and medicinal effects could provide herbal preparations. To test the hypothesis of the effect of one of them – quercetin in different forms - on the carbohydrate metabolism this study has been done. It has been shown that the initial, adsorbed and encapsulated quercetin in a cellulose molecule had a pronounced effect on some parameters of carbohydrate, fat and protein metabolism in rats compared with animals that did not receive this bioflavonoid. The initial quercetin showed a distinct, but short-term, hypoglycemic effect already on the 1-st day of the study, while the surface-adsorbed and cellulose-encapsulated quercetin had a significant effect starting from the 5-th day, but this effect persisted throughout the observation. These hypoglycemic effects of quercetin partly due to the increase of glycogen in the liver and elevation of plasma corticosterone. The other possible mechanisms of quercetin effect on glucose concentration in plasma are proposed.

Keywords: carbohydrate metabolism, diabetes mellitus, quercetin, rat

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Introduction

The incidence of diabetes mellitus (DM) is an acute medical and social problem related to the priorities of national health systems in almost all countries of the world protected by WHO regulations.[1,2] The main treatment options for diabetes, depending on its type, are insulin injections or the use of sulfonylureas and biguanides, which do not cure and do not prevent the occurrence of vascular complications in patients. Therefore, the search for drugs of various nature for the prevention and correction of diabetes and its complications is an urgent task. One of such compounds may be the herbal preparation quercetin, belonging to the family of flavonoids, which has many medicinal properties (anticancer,[3] antioxidant,[4] antiviral,[5,6] etc.), some of which have been confirmed by serious clinical papers. This biological activity is due to the fact that quercetin is an aglycone without a carbohydrate group. Quercetin glycoside is formed by attaching sugar to it – glucose, rhamnose or rutinose - that replaces one of the hydroxyl groups in its structure, usually in position 3, and by subsequent formation of a glycoside bond. These changes affect the solubility, absorption and other effects of quercetin in vivo.[4]

Biologically active polyphenols of the flavonoid family presented in some products of plant origin have recently aroused sharply increased interest.[7-9] Most compounds of this family are quite strong antioxidants.[4] The presence of antioxidant properties suggests that this flavonoid can be used as a promising artificial absorber of free radicals that are generated in vivo and damage tissues during various pathophysiological processes. Thus, it has been shown in animal models that quercetin weakens oxidative stress and cell damage in cases of ischemia/reperfusion,[10,11] ultraviolet radiation,[12] has anti-asthmatic activity,[13,14] inhibits the accumulation of both aldose reductase and polyols in the lens of diabetic mice,[15] et al. In addition, quercetin has demonstrated the ability to significantly reduce fasting glucose levels, improve glucose balance.

Since reactive oxygen species are one of the main damaging factors in many diseases, including diabetes, the therapeutic use of such a non-toxic natural antioxidant drug as quercetin, acting at the level of cells and tissues, is currently the subject of extensive research. However, most researchers focus exclusively on the antioxidant potential of this flavonoid, while little attention is paid to other possibilities of using the drug. The prospects of using quercetin as part of complex drug therapy for the correction of homeostasis and metabolism in DM are of great theoretical and practical interest. The data obtained can be the basis for the introduction of this flavonoid into medical practice, as well as for the synthesis of new effective drugs.

Material and methods

The study was conducted on adult male Sprague-Dawley rats (n=62). All animals were divided into 7 groups: the 1st - control, the 2-nd -control plus quercetin; the rest rats with an experimental alloxan model of DM. To simulate DM, rats were injected with a 10% alloxan solution into the interscapular region at the rate of 0.1 ml/100 g of body weight. Animals of the 1st (n=6) and the 3rd groups (n=9) were kept on standard feed, while rats of the 2nd (n=7), 4th (n=10), 5th (n=10), 6th (n=10) and the 7th (n=10) groups were administered per os quercetin solution at the rate of 5 mg/100 g in a volume of 2% of body weight. The rats of the 2nd and the 4th groups received the initial quercetin, the 5th group - quercetin adsorbed on the surface of the cellulose molecule; the 6th group - quercetin mechanically deposited on cellulose; the 7th group — quercetin encapsulated in a cellulose molecule.

The use of cellulose is due to the fact that the presence of a carbohydrate molecule in the structure of the glycoside quercetin contributes to its better solubility in water compared to the aglycone quercetin.[16] In a thorough review of quercetin studies published at the beginning of this century, Scholz and Williamson concluded that the factors that most affected the bioavailability and absorption of quercetin were the structure of a simple or complex carbohydrate that was added to it, as well as its solubility, which may vary depending on the inclusion of alcohols and fat.[17]

During the post-injection period, all rats on the 1, 3, 5, 7, 9, 11, 13, 15, and the 17th day, blood samples in a volume of 20 µl were taken from the tail after preheating it in warm water to determine the glucose concentration. The concentration of glucose in the blood was determined by electrochemical enzymatic analysis on an automatic glucose analyzer Super GL (Dr. Muller, Germany). At the end of the experiment (on the 17th day after taking quercetin), 5 ml blood samples were taken from the vena cava inferior from animals under ether anesthesia into tubes cooled and treated with sodium-free heparin to determine the concentration of corticosterone by enzyme immunoassay using standard kits on a Multiskan FC tablet ELISA photometer (USA). The biochemical parameters characterizing the protein, lipid, carbohydrate and mineral balance of blood plasma were evaluated using a Mindrey biochemical analyzer (China). Liver samples were taken to determine the glycogen content, followed by a McManus SHIC reaction and measurement of the staining intensity on a Spekol spectrophotometer (Germany) at a wavelength of 430 nm.

The obtained results were processed by mathematical statistics methods using the package "Microsoft Excel 2010" and "Statistica 6.0 for Windows". The analysis was carried out on the basis of calculation of arithmetic averages of general aggregates (M), their errors (± m) and mean square deviations (σ). To identify the significance of the differences between the control and experimental groups, the Wilcoxon-Mann-Whitney criterion was used for independent samples, and in the dynamics of observation for each sample the Student's t-test was used.[18] All experiments were carried out in accordance with the International Recommendations on Biomedical Research using Animals adopted by the International Council of Scientific Societies (CIOMS) in 1985, with Article XI of the Helsinki Declaration of the World Medical Association.

Results and discussion

At the first stage of the study, in order to verify the development of diabetes and assess the hypoglycemic effectiveness of the use of phytopreparations, the glucose concentration in the whole blood of animals was measured after the injection of alloxan, before and during oral administration of quercetin solutions (Table 1). Analysis of glucose levels in the blood of healthy rats with normal carbohydrate metabolism showed that glucose concentration in blood did not change throughout the study (6.9 ± 0.19 mmol/l at the beginning of the study; 7.0 ± 0.42 mmol/l at the 15-th day) (Group 1, the results were not included in the Table 1). It should be noted that the initial quercetin showed a pronounced hypoglycemic effect in control rats already on the 1-st day of the study (baseline 6.7 ± 0.15 mmol/l, the 1-st day after quercetin intake – 5,4 ± 0.11 mmol/l), however, starting from the 3rd day, there was only a tendency to decrease this monosaccharide in the blood (6.3 ± 0.15 mmol/l) (group 2, the results were not included in the Table 1).

Table 1 Changes of glucose concentration in the blood of rats compared to the baseline level, mM/l (M ± m)

№	Groups of animals	Baseline	Days following alloxan injection								
			1	3	5	7	9	11	13	15	17
3	DM	6,5±0,25	18,2±2,6*	23,1±1,4*	25,0±0,6*	22,9±2,8*	25,9±0,5*	25,1±1,4*	24,0±0,5*	25,5±0,6*	23,2±2,1*
4	DM +quercetin	6,8±0,14	11,4±2,7*Δ	19,1±2,6*	20,7±3,3*	18,3±4,8*	19,7±2,8*Δ	19,5±4,8*	19,8±4,8*	21,3±4,7*	-
5	DM+quercetin (adsorbed)	7,2±0,2	20,4±1,3*	21,6±1,0*	20,4±1,5*Δ	16,4±3,1*Δ	17,6±3,3*Δ	16,1±2,5*Δ	16,9±3,4*Δ	12,6±3,1*Δ	15,1±3,1*Δ
6	DM+quercetin (mechanochemical application)	7,3±0,3	24,7±0,1*Δ	21,6±1,0*	21,2±0,1*Δ	22,3±0,5*	25,3±0,2*	24,4±0,2*	22,2±0,1*	16,0±2,2*Δ	22,5±1,7*
7	DM+quercetin (encapsulated)	6,8±0,2	16,2±2,6*	21,2±2,2*	17,9±2,9*Δ	20,1±2,9*	16,3±2,6*Δ	17,8±2,9*Δ	20,2±2,7*	11,8±2,8*Δ	18,9±2,9*

Note (here and after): * – significant differences from similar parameters of the control group (p≤0.05);
Δ – significant differences between the experimental groups and the third group (p≤0.05).

After alloxan injection, the glucose concentration in the blood of animals of all experimental groups (3 – 7) was significantly higher on the 1-st day of observation than in the control and baseline, which indicated the development of DM (Table 1). Adsorbed on the cellulose surface and encapsulated in cellulose, quercetin (groups 5 and 7) statistically significantly reduced blood glucose concentration starting from the 5-th day of observation. The most pronounced hypoglycemic effect was manifested by the bioflavonoid adsorbed on the surface of the cellulose molecule, which persisted throughout the observation. Mechanochemically applied to cellulose quercetin practically did not have a hypoglycemic effect, except for the 5-th and the 15-th days, when this indicator statistically significantly differed from similar parameters of diabetic animals that did not receive bioflavonoid (Table 1).

It can be assumed that the observed delayed hypoglycemic effect in groups 5-7 was associated with a cellulose molecule, which is practically not absorbed in the gastrointestinal tract. Since the concentration of glucose in the blood largely depends on its content in the depot, at the next stage of the work, the level of glycogen in the liver of rats was determined in control, before and after taking quercetin solutions. It was shown that in animals with DM, while taking standard feed, the level of this polysaccharide was significantly lower than in control animals, which is consistent with the literature data.[19-21] However, in rats treated with cellulose-adsorbed and encapsulated quercetin, an increase in the glycogen content was observed almost to the control values (Table 2). Moreover, even in healthy rats, quercetin caused a slight increase in the content of this polysaccharide in the liver. This indicated the effect of the drug on the deposition of excess blood glucose in the liver.

Table 2 Glycogen content in liver of rats, mg/100 g wet tissue weight (M ± m)

No	Animal Groups	Glycogen content
1	Control	402,2±38,1
2	Control + quercetin	462,1±30,3
3	DM	220,6±60,04*
4	DM + quercetin	208,8±53,4*
5	DM + quercetin (adsorbed)	321,5±32,9
6	DM + quercetin (mechanochemical application)	128,1±9,5*
7	DM + quercetin (encapsulated)	327,7±43,8

Note: see Table 1.

A significant role in the regulation of glucose concentration in the blood is played by hormones of the adrenal cortex – glucocorticoids,

the concentration of which, as a rule, increases in diabetes mellitus.[22,23] Therefore, it was further important to evaluate the concentration of corticosterone in the blood plasma of rats as an important glucoregulatory hormone. The results of the evaluation of the effect of quercetins on the level of corticosterone showed that in DM there was an increase in the concentration of this hormone, which indicated a stress reaction in animals.

It should be noted that in all experimental groups that received quercetin solutions as a preparation for correcting DM (except for the initial bioflavonoid), the concentration of corticosterone significantly decreased compared to the same indicator of rats that did not receive the drug – Group 2 (Table 3).

Table 3 The concentration of hormones in the blood of rats with alloxan diabetes (M ± m)

No	Animal Groups	Corticosterone, nmol/l
1	Контроль	70,7±15,3
3	DM	311,03±39,4*
4	DM + quercetin	270,4±57,4*
5	DM + quercetin (adsorbed)	58,3±17,9Δ
6	DM + quercetin (mechanochemical application)	160,9±43,1Δ
7	DM + quercetin (encapsulated)	151,3±56,6Δ

Note: see Table 1.

Disorders of carbohydrate metabolism are usually accompanied by changes in lipid, protein, and mineral metabolism,[24-26] therefore, at the next stage of the work it was important to assess the content of some integral biochemical plasma parameters reflecting these types of metabolism in rats with an alloxan model of DM before and after taking quercetin solutions. Analysis of the data showed that quercetin had no effect on the concentration of the main metabolites of healthy animals (control). In experimental animals that consumed standard feed, there was a significant decrease in the concentration of total protein compared to the control, while the concentration of triglycerides, creatinine, urea and uric acid increased, which indicated disoders in the body not only carbohydrate, but also fat and protein metabolism.

The intake of the initial and mechanochemically applied to the cellulose molecule quercetin contributed to the normalization of such indicators as creatinine, urea, uric acid, total protein, almost to the control values. Adsorbed on the cellulose surface and encapsulated quercetin restored such biochemical parameters as triglycerides, creatinine, urea, uric acid and total protein. It reflected in such homeostatic parameter as osmolarity, an integral characteristic of all osmotically active substances in blood plasma. Osmolarity analysis revealed a statistically significant increase in the studied indicator in all diabetic groups compared to the same indicator in the control group. Quercetin solutions had no effect on osmolarity, probably due to the unequal, and sometimes opposite, effect on various blood metabolites.

Conclusion

Thus, it was found that the initial, adsorbed and encapsulated quercetin in a cellulose molecule had a pronounced effect on some parameters of carbohydrate, fat and protein metabolism in rats compared with animals that did not receive this bioflavonoid. It should be noted that the initial quercetin showed a distinct, but short-term, hypoglycemic effect already on the 1-st day of the study, while the surface-adsorbed and cellulose-encapsulated quercetin had a significant effect starting from the 5-th day, but this effect persisted throughout the observation.

The mechanisms of action of this bioflavonoid on other mechanisms of the regulation of carbohydrate metabolism, in particular, absorption in the gastrointestinal tract, the incretion of other glucoregulatory hormones, glucose excretion by the kidneys, etc., require further study.

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None.

Conflicts of Interest

None.

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