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Development of New Aquaretic Drug Based on Phenolic Glycoside Structure

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Abstract: We studied diuretic and saluretic effects of new synthetic origin phenolic glycosides in comparison with the leader-structure arbutin. Investigation of diuretic and saluretic activity of hydroquinone-O-β-D-glucopyranoside (arbutin) 2-methoxy-4-formylphenyl-O-β-D-glucopyranoside and phenyl-O-β-D-glucopyranoside was conducted on white laboratory rats. Animals received drug with increasing dose over 14 days. Baseline diuresis after administration of 2 mL of distilled water of experimental group accepted as a control. The quantity of urine output was measured a day after administration of the test substances. The concentration of sodium and potassium ions in the urine were determined by flame photometry. The data obtained indicate that investigated glycosides has high diuretic activity. We observed dose-dependent effect of substances. The 2-methoxy-4-formylphenyl-O-β-D-glucopyranoside it is the most promising of the investigated in this study the synthetic compounds.

Key words: Diuretic, saluretic, aquaretic, pheholic glycoside, arbutin, rat

INTRODUCTION

Diuretics are also commonly prescribed for patients with cardiovascular diseases. Diuretics are widely used in the treatment of patients with hypertension as in the elective care (one of the classes of antihypertensive drugs "first line") and in emergencies. Diuretics are used as a "base" class of drugs in the treatment of patients with chronic heart failure; they are also used in different types of heart failure decompensation (including the cardiac asthma, pulmonary edema). Diuretics are used in patients with ascites in liver cirrhosis, nephrotic syndrome in patients with acute and chronic renal lesions.

Most of the diuretics can lead to quite serious complications in spite of its efficiency. This is mainly due to an increased excretion of sodium, potassium, magnesium and chlorine which are involved in the maintenance of water-electrolytic balance. As a result of the loss of electrolytes increases the risk of violations of basic functions of organs. Along with this, there is a possibility metabolic change. Endocrinopathies are essential disadvantages of spironolactone, limiting their use (Gustafson*et al*., 2000).

Considering the complexity and relevance of the problem we have been chosen by the direction of the search for new synthetic diuretics. The leader structure of new group of drug is arbutin or hydroquinone-O-glycoside. It is O-glycoside and this compound encountered in bearberry leaves. Bearberry leaves and cranberries have a diuretic effect due to arbutin. However, upon hydrolysis of arbutin forms toxic hydroquinone. The new compounds should have aquaretic effect and replace existing diuretics are used to treat a variety of chronic diseases. Their use should significantly reduce the violation of water-electrolytic balance in the long course of treatment of pyelonephritis, cystitis, chronic heart failure, chronic renal failure. The aim of this study is the evaluation diuretic activity of new origin synthetic phenolic glycosides, compared in comparison with the leader-structure arbutin.

MATERIALS AND METHODS

Drugs and pharmacological treatments: Arbutin was purchased from Sigma-Aldrich Co. (St. Louis, MO, USA), chloroform (Neochim, Russia).

Chemistry: The experimental molecules for this study were obtained by organic synthesis in the Laboratory of the Department of Biochemical, TPU (Tomsk, Russia).

IR spectra were recorded with IR Fourier spectrophotometer spectrum BX II using KBr disks. The 1H and 13C NMR spectra were recorded on Bruker-300 MMX spectrometer at 300 and 75.5 MHz, respectively, in DMSO-d6 and D_2O-d2 with TMS as an internal standard. The chemical shifts are given in d (parts per million) and the spin-spin coupling constants (J) in hertz. GC-MS

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analysis was performed using Agilent 7890A/5975C GC/MSD instrument, electron energy 70 eV. The ion source temperature was 230°C, with the quadrupole temperature 150°C and evaporator temperature 315°C, employing a 30.000×0.25 mm×0.25 μm HP-5MS fused-silica capillary column. Helium was used as carrier gas at a constant flow of 1 mL/min and an inlet temperature of 315°C. The column temperature mode: 2 min at 70°C, 70-315°C (10°C/min) and 25 min at 315°C. Chloroform was used after drying with P_2O_5.

Animals: Young adults Wistar rats (220-250 g) were obtained from the Institute of Cytology and Genetics SB RAS, Novosibirsk, Russia. Animals were maintained at controlled room temperature with free access to food and water, under a 12 h light/dark cycle. All experimental procedures were performed in accordance with "European convention for the protection of vertebrate animals used for experimental and other scientific purposes".

Diuretic activity: Investigation of diuretic and saluretic activity of hydroquinone-O-β-D-glucopyranoside (arbutin) 2-methoxy-4-formyl phenyl-O-β-D-glucopyranoside and phenyl-O-β-D-glucopyranoside was conducted on white laboratory rats in Vivarium Research Institute of Biological Medicine (Barnaul, Russia). The animals were kept in metabolic cages equipped with a funnel for collection of urine. Rats were on normal diet and free access to water and food. At the start of the experiment were determined baseline parameters diuresis and sodium and potassium concentration in urine. Rats were divided into 3 groups (n = 12). The 1st group was given within 2 weeks hydroquinone-O-β-D-glucopyranoside, the 2nd group 2-methoxy-4-formylphenyl-O-β-D-glucopyranoside, 3rd group O-phenyl-β-D-glucopyranoside. Animals were pretreated orally (po) drugs at doses of 6 mg/kg on the first to 7th days and 17mg/kg on 8-14th days by 2 mL of drinking water. Baseline diuresis after administration of 2 mL of distilled water of experimental group accepted as a control. The quantity of urine output was measured a day after administration of the test substances. The concentration of sodium and potassium ions in the urine were determined by Flame Photometry in the Automated photometer FPA-2-01 (Russia).

Statistical analysis: For *in vivo* studies, the results were expressed as mean±Standard Error Means (SEM). Statistical evaluation of the data was performed using one-way Analysis of Variance (ANOVA) followed by Bonferroni's test. Values of $p<0.05$ were considered statistically significant.

RESULTS

NMR analysis: 1H NMR (300 MHz, D_2O), δ: 3.23-3.83 (6H, m, H-2', H-3', H-4', H-5', H-6'a, H-6'b); 3.79 (3H, **c**, CH_3); 5.12 (1H, m, H-1'); 7.12(1H, d, J = 1.5 Hz, H-6); 7.36 (1H, c, H-3); 7.41 (2H, d, H-5, J = 1.5 Hz); 9.62 (1H, **c**, COH). 13c NMR (D_2O), δ, : 55.3 (CH_3); 59.9 (CH_2, C6'); 68.7 (CH, C-4'); 72.1 (CH, C-2'); 74.9(CH, C-5'); 75.7(CH, C-3'); 99.0(CH, C-1'); 110.8 (CH, C-3); 114.3(CH, C-6); 126.1 (CH, C-5); 131.0 (C, C-4); 148.8(C, C-1); 151.0 (C, C-2); 194.0 (C, COH).

Diuretic activity: When administered hydroquinone O-β-D-glucopyranoside at a dose of 6 mg/kg (Fig. 1) was an increase in urine output was almost 2 times on study days 4-6. While sodium excretion decreased by 34% compared with the control throughout the experiment. In addition, the potassium loss amounted 174% on the 1st day, gradually decreasing to 152% by day 7. Increasing doses of hydroquinone-O-β-D-glucopyranoside to 17 mg/kg, caused an increase in water release by the kidneys which peaked to a study's 7 day, exceeding the control performance is >5 times. Sodium excretion decreased by 33%. Loss of potassium increased by 2 times relative to the baseline (Table 1).

The 2-methoxy-4-formylphenyl-O-β-D-glucopyranoside at a dose of 6 mg/kg (Fig. 1) was significantly increased diuresis in average by 166% (4-7 days). Changes of sodium excretion was not significant. Potassium excretion increased by 36%. Oral administration of 17 mg/kg (Fig. 2) 2-methoxy-4-formylphenyl-O-β-D-glucopyranoside increased daily urine output >2 times. Sodium losses were not significant. Potassium excretion reached the value of 139% on day 5 of the experiment (Table 2 and Fig. 2).

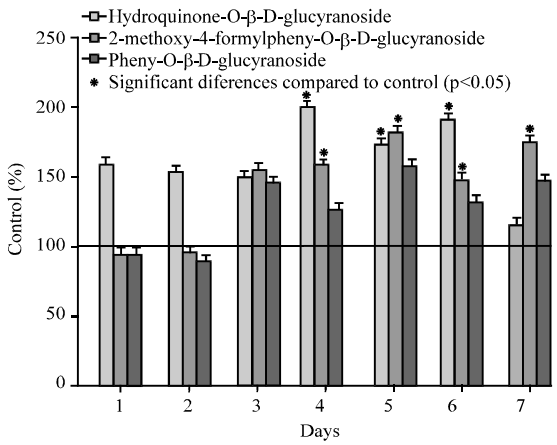

Fig. 1: Compare diuretic activity of the test substances (6 mg/kg intragastrically, solvent purified water)

Table 1: Effect of test substances on urinary excretion of electrolytes (Na+, sluretic index, 6 mg/kg intragastrically conrtol = 1.0)

	Substances		
Days	Hydroquinone-O-β-D-glucopyranoside	2-methoxy-4-formylphenyl-O-β-D-glucopyranoside	Phenyl-O-β-D-glucopyranoside
1	1.40	0.53	1.55
3	1.00	1.48	1.03
5	1.24	2.53	0.99
7	0.60	1.12	1.10

Table 2: Effect of test substances on urinary excretion of electrolytes (Na+, saluretic index, 17 mg/kg intragastrically conrtol = 1.0)

	Substances		
Days	Hydroquinone-O-β-D-glucopyranoside	2-methoxy-4-formylphenyl-O-β-D-glucopyranoside	Phenyl-O-β-D-glucopyranoside
1	0.63	0.97	1.17
3	1.05	0.54	1.71
5	0.66	1.02	1.99
7	1.06	0.69	1.24

Table 3: Effect of test substances on urinary excretion of electrolytes (K+, saluretic index, 6 mg/kg intragastrically conrto l= 1.0)

	Substances		
Days	Hydroquinone-O-β-D-glucopyranoside	2-methoxy-4-formylphenyl-O-β-D-glucopyranoside	Phenyl-O-β-D-glucopyranoside
1	1.74	0.99	1.26
3	1.62	1.35	2.02
5	1.75	1.38	0.92
7	1.52	1.02	1.09

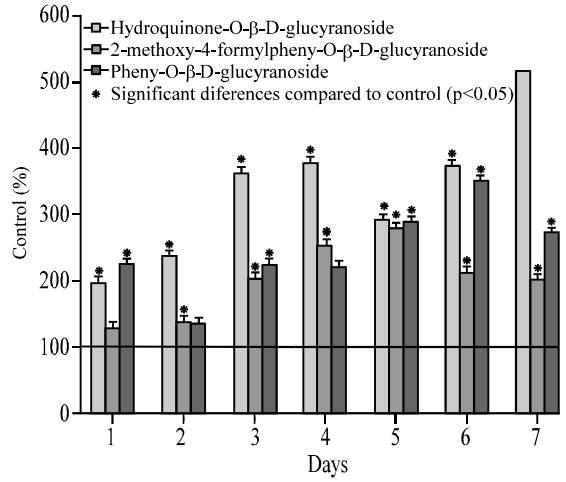

Fig. 2: Compare diuretic activity of the test substances (17 mg kg intragastrically, solvent-purified water)

Oral administration of the phenyl-O-β-D-glucopyranoside at a dose of 6 mg/kg (Fig. 1) caused no significant changes in renal function parameters except for potassium excretion is increased by 2 times at 3rd day administration of the substance. Other values of diuresis after administration of phenyl-O-β-D-glucopyranoside in a dose of 17 mg/kg were detected (Fig. 2) it increased

Table 4: Effect of test substances on urinary excretion of electrolytes (K+, saluretic index, 17 mg/kg intragastrically, conrtol = 1.0)

	Substances		
Days	Hydroquinone-O-β-D-glucopyranoside	2-methoxy-4-formylphenyl-O-β-D-glucopyranoside	Phenyl-O-β-D-glucopyranoside
1	1.59	1.14	1.17
3	2.39	1.01	1.71
5	1.91	1.39	1.99
7	2.64	1.28	1.24

2.7 times. Indicators sodium excretion were not significant. Potassium loss increased 2.8 times when administered phenyl-O-β-D-glucopyranoside in a dose of 17 mg/kg (Table 3 and 4).

DISCUSSION

The highest diuretic effect was detected of hydroquinone-O-β-D-glucopyranoside. Probably, the activity due to hydroxyl group in the para-position which is an active hydrogen functional group donor for the target protein. Phenyl-O-β-D-glucopyranoside provided 80% more pronounced potassium excretion, compared with hydroquinone-O-β-D-glucopyranoside and 140% compared to 2-methoxy-4-formylphenyl-O-β-D-glucopyranoside. Safety of substances is a crucial factor in the choice of agent for the manufacture of drug. Phenyl-O-β-D-glucopyranoside during the hydrolysis forms a phenol. This compound is toxic to the organism. Hydroquinone-O-β-D-glucopyranoside, undergoing hydrolysis to forms a toxic metabolite-hydroquinone.

The findings suggest about high diuretic activity of investigated glycosides. At the same time, observed a dose-dependent character of the influence of substances. Such a correlation was characteristic for all glycosides with diuretic activity. In this relation saluretic activity, unambiguous dependence have been identified. The 2-methoxy-4-formylphenyl-O-β-D-glucopyranoside is the most promising of the investigated in this study the synthetic compounds because in the hydrolysis of the glycoside formed by glucose and vanillin. Glucose is known to be non-toxic. Vanillin in turn, even when administered at high doses (up to 300 mg/kg) has no toxic properties (Lirdprapamongkol *et al*., 2009, 2010) further data are available in the presence of vanillin onkoprotektor properties (Ho *et al*., 2011; Siegers *et al*., 2003). Note that the same vanillin possesses anti-inflammatory and bacteriostatic activity in inflammatory bowel disease.

CONCLUSION

The 2-methoxy-4-formylphenyl-O-β-D-glucopyranoside has a mild diuretic action, independent of the excretion of sodium and potassium ions.

REFERENCES

Gustafson, D.L., H.R. Franz, A.M. Ueno, C.J. Smith and D.J. Doolittle *et al*., 2000. Vanillin (3-methoxy-4-hydroxybenzaldehyde) inhibits mutation induced by hydrogen peroxide, N-methyl-N-nitrosoguanidine and mitomycin C but not 137Cs ?-radiation at the CD59 locus in human-hamster hybrid AL cells. Mutagen., 15: 207-213.

Ho, K., L.S. Yazan, N. Ismail and M. Ismail, 2011. Toxicology study of vanillin on rats via oral and intra-peritoneal administration. Food Chem. Toxicol., 49: 25-30.

Lirdprapamongkol, K., H. Sakurai, S. Suzuki, K. Koizumi and O. Prangsaengtong *et al*., 2010. Vanillin enhances TRAIL-induced apoptosis in cancer cells through inhibition of NF-KB activation. Vivo, 24: 501-506.

Lirdprapamongkol, K., J.P. Kramb, T. Suthiphongchai, R. Surarit and C. Srisomsap *et al*., 2009. Vanillin suppresses metastatic potential of human cancer cells through PI3K inhibition and decreases angiogenesis *in vivo*. J. Agric. Food Chem., 57: 3055-3063.

Siegers, C., C. Bodinet, S.S. Ali and C.P. Siegers, 2003. Bacterial deconjugation of arbutin by Escherichia coli. Phytomedicine, 10: 58-60.