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Role of Sugar Segments of Molecules in the Mechanism of Realization of the Diuretic Effect of Phenolic Glycosides

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Abstract: We studied diuretic and saluretic effects of new synthetic origin phenolic glycosides and their aglicones. Investigation of diuretic and saluretic activity of of 4-nitrophenyl-β-D-glucopyranoside, hydroquinone-O-β-D-glucopyranoside (arbutin) and their aglycon-4-nitrophenol and hydroquinone was conducted on white laboratory rats in vivarium Animals received drug 7 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. Phenolic glycosides have a pronounced diuretic effect as opposed to their aglycones in rats.

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

INTRODUCTION

Phenolic glycosides are sufficiently widespread class of chemical compounds contained in medicinal plants. Currently, researchers are studying the various countries the chemical composition and pharmacological activity of plants growing in certain areas. So, fruits of *Idesia polycarpa* contain idesin salicylate and 2-hydroxyphenol-1-O-beta-D-glucopyranosyl-(6-->1)-alpha-L-rhamnopyranoside, idescarpin, idesin, 1-hydroxy-6-oxocyclohex-2-enecarboxylic acid methyl ester and salirepin, all compound inhibited lipopolysaccharide-induced nitric oxide production in BV2 microglia (Kim *et al*., 2007). GreVillea "Poorinda Queen" have significant antimalarial activity (Ovenden *et al*., 2010). The antioxidant activity is detected at the majority plants containing the phenolic glycosides (Zhang *et al*., 2006; Braca *et al*., 2003; Marino *et al*., 2007; 2012). Also, scientists credited with phenolic glycosides such types of pharmacological activity as the anty complementary activity (Li *et al*., 2013), antidepressant activity (Zhou *et al*., 2016), antiproteasomal activity (Gulcemal *et al*., 2010), antitumor activity (Dai and Mumper, 2010) and anti-inflammatory activity (Cheenpracha *et al*., 2010; Zhang *et al*., 2015; Li *et al*., 2014; Jianbo and Jiang, 2005). However, we are interested in plants that contain phenolic glycosides-arbutin. We know that *Arctostaphylos uvaursi and Vaccinium vitis* idaea have a diuretic activity (Beaux *et al*., 1999; Kalinina *et al*., 2014). Is contemplated that the effect of these herbal diuretics is to enhance glomerular filtration rate and an increase in the formation of primary urine due to increased renal blood flow and (or) the acceleration of osmotic processes (Kisileva *et al*., 2006). Many researchers believe, these types of actions are characteristic not arbutin, contained in a medicinal plant and inherent hydroquinone which is released in the enzymatic hydrolysis of arbutin by *Escherichia coli* in the intestinal tract (Siegers *et al*., 2003).

The aim of this study is compare of diuretic and saluretic activity of 4-nitrophenyl-β-D-glucopyranoside, hydroquinone-O-β-D-glucopyranoside (arbutin) and their aglycones-4-nitrophenol and hydroquinone on rats.

MATERIALS AND METHODS

Drugs and pharmacological treatments: Arbutin (hydroquinone-O-β-D-glucopyranoside), 4-nitrophenol and hydroquinone was purchased from Sigma-Aldrich Co. (St. Louis, MO, USA).

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

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DMSO-d6 and D2O-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 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 SBRAS, 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 of 4-nitrophenyl-β-D-glucopyranoside, hydroquinone-O-β-D-glucopyranoside (arbutin) and their aglycones-4-nitrophenol and hydroquinone 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 4 groups (n = 12). The 1st group was given hydroquinone-O-β-D-glucopyranoside, the 2nd group-4-nitrophenyl-β-D-glucopyranoside, 3rd group-4-nitrophenol, 4th group-hydroquinone. Animals were pretreated orally (p.o.) drugs at doses of 54 mmol/kg by 2 mL of drinking water for 7 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 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 AND DISCUSSION

Chemistry: To a stirred solution of a 2, 3, 4, 6-tetra-O-acetyl-α-D-glucopyranosyl bromide (1 equiv., 0.5 g) and a 4-nitrophenol (1.1 equiv., 0.18 g) in 5 mL of acetone was added NaOH (1.1 equiv., 0.05 g) in 5 mL of water. The reaction was stirred at room temperature and monitored by TLC then extracted twice with chloform. The combined organic layers were wased twice 10% NaOH and water then dried over $MgSO_4$ and concentrated in vacuo to give oil. The oil was crystallized in ethanol. Yield: 42%, mp: 175°C (Lit. 175-178°C (Baggett and Marsden, 1983).

1H NMR (300 MHz, $CDCl_3$) δ: 2.04, 2.05, 2.06, 2.07 (4×3H, s, $COCH_3$); 3.91 (1H, m, H-5'); 4.15-4.31 (2H, m, H-6'a, H-6'b); 5.14-5.30 (4H, m, H-1', H-2', H-3', H-4'); 7.06 (2H, d, J = 9.0 Hz, H-2, H-6); 8.19 (2H, d, H-3, H-5, J = 9.3 Hz). 13C NMR (50 MHz, $CDCl_3$), δ: 20.5 (4×CH_3, $COCH_3$); 61.8 (CH_2, C6'); 67.9 (CH, C-4'); 70.8 (CH, C-2'); 72.3(2×CH, C-5', C-3'); 98.0 (CH, C-1'); 116.6 (2×CH, C-2, C-6); 125.7 (2×CH, C-3, C-5); 143.2(C, C-4); 161.1 (C, C-1); 169.1, 169.2, 170.0, 170.3 (4×C, $COCH_3$).

To a suspension of p-nitrophenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyde (1 equiv., 2 g) in 8 vL of methanol was added 5 mL of 5% MeONa in methanol. The reaction was stirred at room temperature 12 h then methanol was evaporated in vacuo. Obtained product was recrystallized in methanol. Yield: 93%, mp: 163°C (Lit. 165-166°C).

1H NMR (300 MHz, D2O) δ: 3.42-3.70 (5H, m, H-2', H-3', H-4', H-5', H-6'b); 3.84 (1H, d, H-6' a, J = 12.0 Hz); 5.1 (1H, m, H-1'); 7.13 (2H, d, J = 8.1 Hz, H-2, H-6); 8.14 (2H, d, H-3, H-5, J = 8.4 Hz); 13C NMR (50 MHz, D2O), δ: 60.4 (CH_2, C6'); 69.3 (CH, C-4'); 72.7 (CH, C-2'); 75.5(CH, C-5'), 76,2 (CH, C-3'); 99.4 (CH, C-1'); 116.4 (2×CH, C-2, C-6); 126.0 (2×CH, C-3, C-5); 142.42 (C, C-4); 161.7 (C, C-1).

Diuretic activity: Pharmacological studies have shown that 4-nitrophenyl-O-β-D-glucopyranoside and its aglycone 4-nitrophenol in the 1st day of administration of the daily urine output increases by 2.4 times while its aglycone only 1.2 times compared with the control (Table 1).

Maximum diuretic effect in a 4-nitrophenyl-O-β-D-glucopyranoside was achieved on the second day of administration, while the 4-nitrophenol showed maximal effect only on the fifth day of administration.

According to Table 2 shows that the excretion of sodium ions under the influence of 4, nitrophenyl-O-β-D-glucopyranoside in different days was not significantly changed. The excretion of potassium ions throughout the experiment with the introduction 4 nitrophenyl-O-β-D-glucopyranoside was higher than the control, on average,

Table 1: Compare diuretic and saluretic activities of the 4-nitrophenyl-o-β-D-glucopyranoside and 4-nitrophenol (54 mmol/kg, solvent-purified water, n = 12)

	4-nitrophenyl-o-β-D-glucopyranoside		
		Excretion of ions (mg/L)	
Days	Diuresis (mL/day)	Na+	Na+
Control	4.56±0.69	20.55±5.70	278.59±23.02
1	11.00±1.55*	21.87±8.77	392.12±98.66
2	13.07±2.00*		
3	12.20±1.89*	22.90±6.14	368.65±39.28*
4	11.40±2.60*		
5	11.61±2.27*	28.83±6.53	346.68±35.00
6	12.45±2.14*		
7	10.84±1.70*	20.44±7.6	366.30±21.78*

Table 2: 4-Nitrophenol activities

	4-Nitrophenol		
		Excretion of ions (mg/L)	
Days	Diuresis (mL/day)	Na+	Na+
Control	5.5±1.2	479±94.70	7.7±2.24
1	6.6±1.5	479.23±94.70	7.69±2.24
2	6.1±1.0	227.84±14.8*	2.1±0.24*
3	5.9±1.4	–	–
4	7.6±1.9	226.18±41.7*	2.03±0.3*
5	9.6±2.1	–	–
6	9.3±2.4	243.11±18.65	3.13±0.4
7	6.4±1.6	–	–

*Significant differences compared to control ($p<0.05$)

1.4 times ($p<0.05$) While the management of 4-nitrophenol sodium and potassium excretion It was lower than control values in the 2-2.5 times throughout the experiment but the data are not reliable.

With the introduction of hydroquinone and arbutin, urine output increased significantly from the first day of administration and remained high until the end of the experiment. It should be noted that despite the fact that both substances showed a diuretic effect in arbutin was higher. Since, the maximum urine excretion when administered to the control was higher than arbutin 5 times, hydroquinone-3 times.

As shown in Table 3 administration of test substances did not cause natriuretic effect. A study on some days even reduced sodium excretion.

The following results Table 4 were obtained by evaluating the effect of test substances on the excretion of potassium ions: arbutin potassium excretion increased significantly on the first day of administration and until completion of the experiment. Hydroquinone, on the contrary has no effect on potassium excretion.

Data analysis has shown that greater diuretic activity in both experiments has glycoside than its aglycon. Obviously, an increase in urine output was caused by the presence in the structure of the sugar segment which has a complicated structure and is capable of providing

Table 3: Compare diuretic and saluretic activities of the hydroquinone-O-β-D-glucopyranoside and hydroquinone (54 mmol/kg, solvent-purified water, n = 12)

	Hydroquinone-O-β-D-glucopyranoside		
		Excretion of ions (mg/L)	
Days	Diuresis (mL/day)	Na+	Na+
Control	3.3±0.63	6.7±1.03	149.0±35.09
1	6.4±1.08*	4.2±0.5*	236.2±31.29*
2	7.8±1.06*	–	–
3	11.8±1.38*	7.0±1.19	356.0±37.04*
4	12.4±2.29*	–	–
5	9.6±1.38*	4.4±0.89*	284.5±42.36*
6	12.2±1.32*	–	–
7	16.9±1.14*	7.1±1.09	393.8±18.38*

Table 4: Activities of hydroquinone

	Hydroquinone		
		Excretion of ions (mg/L)	
Days	Diuresis (mL/day)	Na+	Na+
Control	3.6±0.61	11.5±2.19	225.3±26.47
1	9.2±1.88*	6.2±1.02*	292.1±42.03
2	8.2±1.84*	5.8±1.03*	312.8±41.52
3	9.1±2.18*	–	–
4	10.9±2.19*	4.2±0.87*	273.8±34.26
5	8.8±1.95*	–	–
6	9.4±1.79*	5.2±0.92*	279.4±44.09
7	8.8±1.93*	–	–

*Significant differences compared to control ($p<0.05$)

high selectivity to the molecule presumed target ligand. It should be noted that unlike classical diuretics studied molecule increases the amount of daily urinary excretion from increasing regardless of electrolytes and diuresis values ion concentration. Thus, it can be assumed that the 4-nitro-phenyl-O-β-D-glucopyranoside and hydroquinone-O-β-D-glucopyranoside not have a direct impact on NKCC, NCC, KCC transporters in the renal tubules. Perhaps investigated glycosides affect the secretion of Glucagon-Like Peptide 1 (GLP-1). The slight increase in the excretion of sodium ions can be explained by the fact that GLP-1 has a direct effect on the Na+/H+-transport in the proximal tubules of the kidney. Glucose serving as glucone in the molecule of the glycoside may significantly affect the formation of the complex "target ligand" as 4-nitrophenol and hydroquinone without sugar segment has a significantly lower diuretic activity. You can make the assumption that the glucose can play the role of carrier molecules for further metabolism and the pharmacological action of rendering using the Na+/glucose cotransporter in small intestine (Mizuma *et al*., 2000).

CONCLUSION

Phenolic glycosides have a pronounced diuretic effect as opposed to their aglycones in rats.

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