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New molecular complex of ammonium glycyrrhizate with rutin

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Abstract

A new 1:1 molecular complex of triterpene glycoside ammonium glycyrrhizate (GC) with flavonoid glycoside rutin (Rut) was obtained in aqueous ethanol. The stability constant $(9.7\pm0.2)\cdot10^4$ $(mol/L)^{-1}$ was calculated for the complex via isomolar curves. The complexation was studied by UV- and ATR IR-Fourier spectroscopy and a method of isomolar series. The hydrogen bonds and hydrophobic interactions are formed in the molecular complex. A preliminary antioxidant activity assessment of the complex was made.

Keywords

triterpene glycosides
ammonium glycyrrhizate
rutin
molecular complex
antioxidant capacity

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1. Introduction

Rutin (Rut; Fig. 1) is one of the most famous flavonols and glycosides [1]. Its aglycone is quercetin. Found in different plants, Rut has P-vitamin activity and exhibits antimicrobial, antioxidant, anti-inflammatory, antidiabetic, antispasmodic, antisclerotic, diuretic, and anticancer effects [1]. Rut has a low solubility in water and limited membrane permeability [1]. The therapeutic effect of Rut is limited due to its bioavailability [1]. The study [2] showed that the solubility and bioavailability of bioactive compounds can be significantly increased by their molecular complexation with triterpene glycosides. Triterpene saponins are amphiphilic multidentate ligands that are capable of molecular complexation with both polar and non-polar fragments of other molecules [2].

Glycyrrhizic acid (GA) and its monoammonium salt (ammonium glycyrrhizate, glycyram, GC; Fig. 1) are widely used as complexing agents [2–6]. GA is the main triterpene saponin of licorice roots [2]. GA increases permeability of cell membranes [5]. Previously, we studied the molecular complex of quercetin with GC [6]. However, molecular complexes of Rut with GC have not been described. This article reports the preparation of a new molecular complex of GC with Rut.

2. Experimental

GC (purity ≥95% by high-performance liquid chromatography (HPLC)) was purchased from Calbiochem. Other chemicals of the highest grade of purity were obtained from Sigma-Aldrich.

The isomolar series were prepared by mixing 10^{-4} mol/L solutions of GC and Rut in 70% aqueous ethanol (v/v) with continuous stirring at 25 °C for 40 min. Spectroscopic analysis of isomolar series was performed on a LEKI SS2110UV spectrophotometer using a quartz cuvette (l = 1 cm) at 25 °C. Stability constant of the complex was calculated according to the A.K. Babko method based on the isomolar curves [5, 7].

The complex of Rut with GC was preparatively obtained by the liquid-phase method. For this purpose, 1 mmol of the substances was mixed with 50 mL of 70% aqueous ethanol (v/v). The obtained mixture was incubated with continuous stirring at 50 °C for 1.5 h. The organic solvent was removed by vacuuming. The synthesized complex was analyzed by IR spectroscopy. The IR spectra were recorded on a Simex FT-801 IR-Fourier spectrometer (Russia) in the 4000–550 cm^{-1} region (spectral resolution 4 cm^{-1}; 25 scans) using the ATR accessory with a diamante crystal plate.

IR spectrum of Rut (ν, cm^{-1}): 3415 (OH), 3343 (OH), 2954 (CH), 2914 (CH), 2847 (CH), 1656 (C=O), 1596 (C=C_{Ar}), 1572 (C=C_{Ar}), 1552 (C=C_{Ar}), 1502 (C=C_{Ar}), 1453 (C=C_{Ar}, CH), 1426 (CH), 1405 (C–OH), 1360 (C–OH, CH), 1313 (CH), 1294 (C–O–C, C–OH), 1234 (C–O–C, C–OH), 1203 (C–O–C, C–OH), 1168 (C–O–C, C–OH), 1149 (C–O–C, C–OH), 1123 (C–O–C, C–OH), 1093 (C–O–C, C–OH), 1059 (C–O–C, C–OH), 1041 (C–O–C, C–OH), 1013 (C–O–C, C–OH), 999 (C–O–C, C–OH), 967 (CH), 943 (CH), 910 (monosaccharide ring), 880 (CH), 848 (CH), 826 (CH), 807 (CH), 794 (CH), 727 (CH), 719 (CH), 707 (CH), 688 (CH), 655 (OH), 629 (CH), 594 (CH).

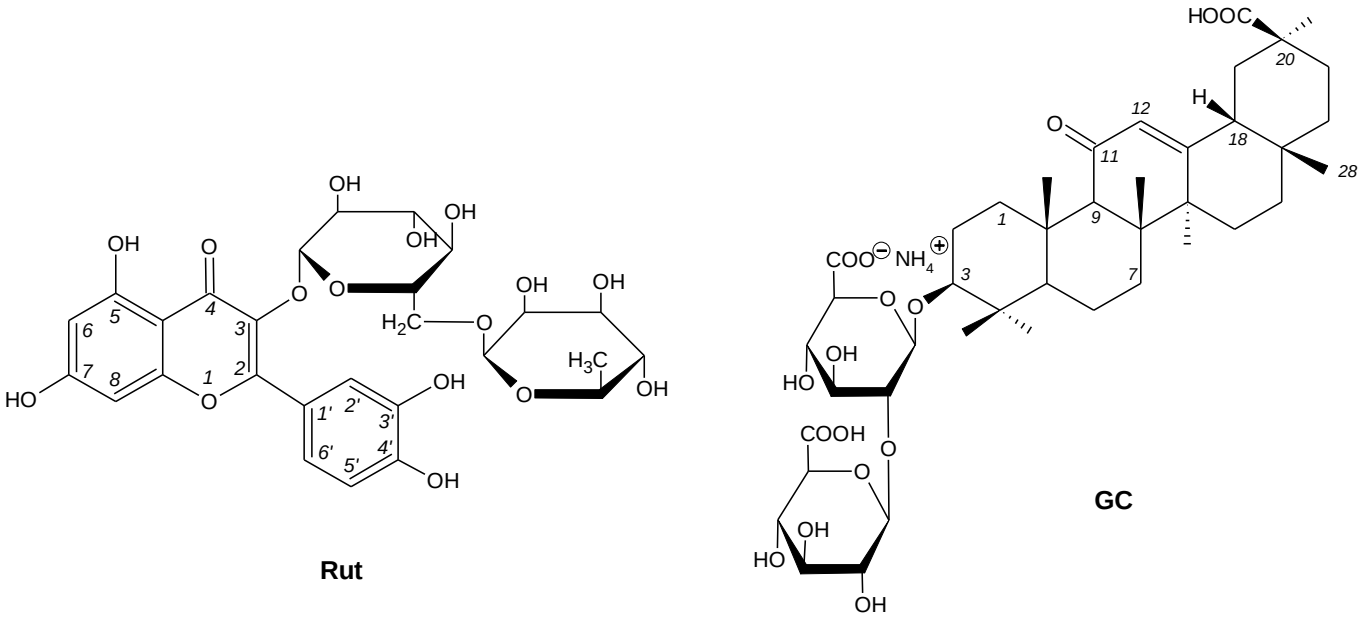

Fig. 1 Structures of Rut and GC

IR spectrum of GC (ν, cm^{-1}): 3212 (OH, NH), 2944 (CH), 2928 (CH), 2911 (CH), 2862 (CH), 1726 (C=O), 1710 (C=O), 1692 (C=O), 1642 (C(11)=O, C=C), 1588 (COO^-), 1453 (CH_2, CH_3), 1428 (NH_4^+), 1414 (COO^-), 1390 (CH), 1358 (CH), 1350 (CH), 1324 (CH), 1304 (CH), 1279 (CH), 1258 (CH), 1211 (CH), 1162 (C–O–C, C–OH), 1032 (C–O–C, C–OH),980 (=CH), 946 (CH), 918 (monosaccharide ring), 879 (CH), 868 (CH), 818 (CH), 786 (CH), 749 (CH), 692 (CH), 684 (CH), 677 (=CH), 657 (OH).

IR spectrum of the complex of Rut with GC (ν, cm^{-1}): 3284 (OH, NH), 2956 (CH), 2919 (CH), 2850 (CH), 1730 ($C=O_{GC}$), 1715 ($C=O_{GC}$), 1682 ($C=O_{GC}$), 1639 ($C=O_{Rut}$), 1584 (COO^-, $C=C_{Ar}$), 1509 ($C=C_{Ar}$), 1451 ($C=C_{Ar}$, CH), 1424 (NH_4^+), 1411 (COO^-), 1360 (C–OH, CH), 1301 (C–O–C, C–OH, CH), 1275 (C–O–C, C–OH, CH), 1235 (C–O–C, C–OH), 1201 (C–O–C, C–OH), 1168 (C–O–C, C–OH), 1073 (C–O–C, C–OH), 1047 (C–O–C, C–OH), 1030 C–O–C, C–OH), 982 (=CH), 929 (CH), 878 (CH), 806 (CH), 786 CH), 717 (CH), 691 (CH), 655 (OH), 598 (CH).

Antioxidant activity was studied on a Photochem analyzer (Analytik Jena AG, Germany). Determination of antioxidant capacity of lipid soluble compounds (ACL) and water soluble compounds (ACW) was carried out according to the manufacturer's standard protocols. ACW = 161.2 nM and ACL = 157.3 nM (in terms of trolox for 49.5 mg/L solutions of Rut–GC complex in 70% aqueous ethanol (v/v)).

3. Results and discussion

The composition of the complex of GC with Rut was determined by the isomolar series method (Figs. 2, 3). This method gave a molar ratio ≈1.0 at 258 nm, which corresponded to a 1:1 complex (Fig. 3). In addition, the isomolar curve shows a clear minimum at 361 nm at a 1:1 ratio of components (Fig. 3). Such ratio was obtained for complexes of GA and GC with several drugs [2]. However, a different composition (1:2) was found in the complex of GC with quercetin [6]. Due to hypsochromic shift, the absorption maximum of the solutions decreases from 258 to 252 nm (Fig. 2).

Stability constant of the complex (K_{GC-Rut} = (9.7±0.2)·10^4 $(mol/L)^{-1}$) was calculated based on the isomolar curves at 258 nm by A.K. Babko method. The previously obtained 1:1 molecular complexes of different bioactive compounds with GC had stability constants of 10^3–10^5 $(mol/L)^{-1}$ [2].

ATR FT-IR spectra of GC and Rut complex show low-frequency shifts of the absorption band of stretching vibrations of O–H bonds in Rut from 3415 and 3343 cm^{-1} to 3284 cm^{-1}.

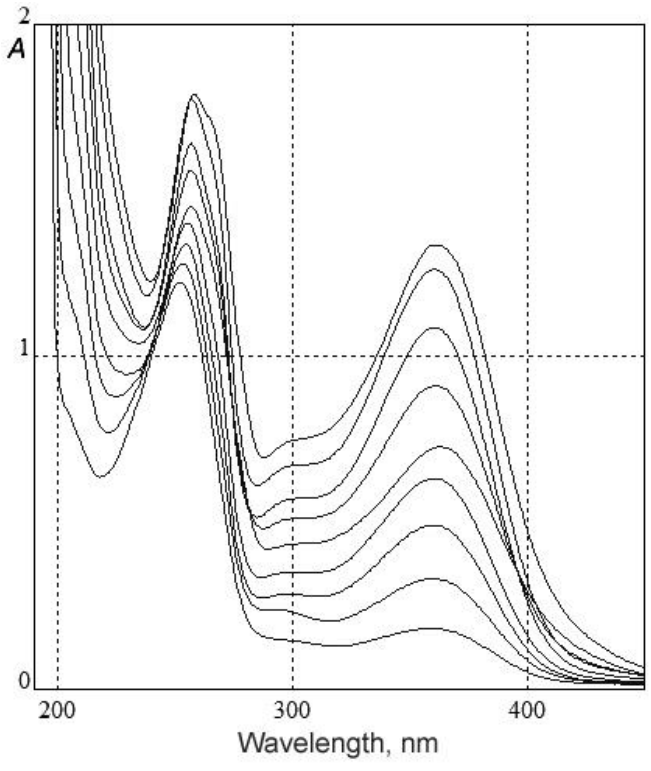

Fig. 2 Absorption curves of isomolar series of solutions at 25 °C

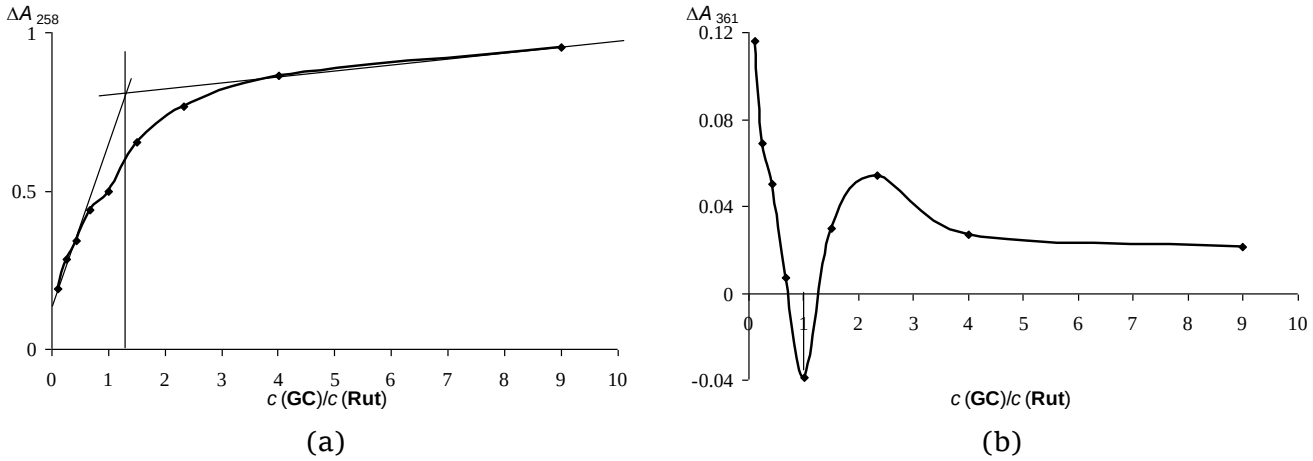

Fig. 3 Optical density change ΔA as a function of component ratio of isomolar series at 258 nm (a) and at 361 nm (b)

Such changes in the spectra confirm the formation of hydrogen bonds.

IR spectrum of complex shows certain changes related to stretching vibrations, absorption bands of C–O bonds in C–O–C and C–OH groups, for example 1059→1047 cm^{-1} for Rut, 1162→1168 cm^{-1} for GC. The presence of low-frequency shifts of C=O stretching vibrations, absorption band is indicative of C=O groups of Rut and GC involvement in hydrogen bonding: 1656→1639 cm^{-1} for Rut and 1692→1682 cm^{-1} for GC.

In addition, the IR spectra show shifts of the main absorption bands of CH bonds, stretching vibrations, which can be caused by hydrophobic interactions in the complex. Their presence explains the stability of the molecular complex of GC with Rut.

Rut, GA and some complexes of GA have antioxidant activity [1, 8, 9]. For example, the antioxidant capacity of complexes of uracil derivatives with GA was studied in several oxidative systems, where they showed a higher activity than ionol [8].

A preliminary study of Rut–GC complex antioxidant activity was performed. At the same time, the analysis of the complex antioxidant capacity (in terms of trolox) showed an increase of ACW by 7.31%, but a slight decrease of ACL by 2.73% in comparison with the Rut standard.

4. Conclusions

A joint molecular complex of triterpene and flavonoid glycosides was obtained for the first time. The composition of the complex of Rut with GC is 1:1. The complex has sufficient stability and is formed by hydrogen bonds ($C{=}O_{GC}...H{-}O_{Rut}$ and $C{=}O_{Rut}...H{-}O_{GC}$) and hydrophobic contacts. Complexation of Rut with GC can improve its bioavailability and membrane permeability, and expand the spectrum of biological activity.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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