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MOLECULAR COMPLEXATION OF IVY AND LICORICE SAPONINS WITH SOME DRUGS OF AROMATIC NATURE

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The molecular complexation of monoammonium glycyrrhizate (glycyrram) with sildenafil citrate, and hederagenin 3-*O*-α-*L*-rhamnopyranosyl-(1→2)-*O*-α-*L*-arabinopyranoside (α-hederin) and its 28-*O*-α-*L*-rhamnopyranosyl-(1→4)-*O*-β-*D*-glucopyranosyl-(1→6)-*O*-β-*D*-glucopyranosyl ester (hederasaponin C) with sildenafil citrate and caffeine was described. The questions of determination of complexes composition, their biological activity, and intermolecular interactions at complexation are discussed.
Keywords: triterpene glycosides, α-hederin, hederasaponin C, monoammonium glycyrrhizate (glycyrram), sildenafil citrate, caffeine, supramolecular complex, biological activity.

Today the molecular complexation of saponins and different biologically active molecules is widely studied. The great interest to these supramolecular products is first and foremost caused by the possibility of new drugs composition by means of drug dose reduction, bioavailability and decomposition resistance increasement, the action prolongation, and expansion of biological activity spectrum of pharmacones [1, 2].

Triterpene glycosides are the most promising natural compounds for molecular encapsulation of drugs. This approach has been examined mainly for glycyrrhizic acid (3-O-β-*D*-glucuronopyranosyl-(1→2)-O-β-*D*-glucuronopyranoside of glycyrrhetinic acid), the main triterpene glycoside of the licorice roots. Molecular complexes of glycyrrhizic acid with pyrimidine derivatives, nonsteroid anti-inflammatory drugs, prostaglandins, cardioactive and psychotropic drugs were prepared. Besides, the complexes of acantophylloside B isolated from *Acanthophyllum gypsophyloides* roots were prepared with prostaglandins [1, 2].

Recently, triterpene glycosides α-hederin (glycoside **1**) and hederasaponin C (glycoside **2**) have been suggested as prospective molecular carrier of biologically active substances and medicines (Fig. 1) [3]. Glycoside **1** is 3-O-α-*L*-rhamnopyranosyl-(1→2)-O-α-*L*-arabinopyranoside of hederagenin, and **2** is 3-O-α-*L*-rhamnopyranosyl-(1→2)-O-α-*L*-arabinopyranosyl-28-O-α-*L*-rhamnopyranosyl-(1→4)-O-β-*D*-glucopyranosyl-(1→6)-O-β-*D*-glucopyranoside of hederagenin. Glycosides **1** and **2** are one of the most widespread saponins of the plants from family Araliaceae Juss. They were discovered in different species of genus *Hedera* and *Kalopanax*, in *Aralia elata* and *Acanthopanax*

sieboldianus [4–6]. Glycoside **1** is also discovered in *Polyscias dichroostachya* [4], and **2** – in *Schefflera octophylla* [7]. Glycoside **2** is converted into **1** by esterases.

Triterpene glycosides **1** and **2** are the components of the cough medicines hedelix [8, 9], prospan [4, 8, 10], pektolvan *Hedera helix* [11], hederin [12] and others. These medicines contain extract of *Hedera helix* L. leaves. *Hedera helix* leaves have been used as cough medicine European ethnoscience for several centuries [4].

Monoammonium glycyrrhizate (glycyrram, compound **3**, Fig. 1) is used as anti-inflammatory and antiallergenic drug [13] and solubilized some drugs [14]. Molecular complexes of **3** with sulfanilamides, gossypol, salsolidine, β-cyclodextrin, and other compounds were recently prepared [15, 16].

In this paper the molecular complexes of **1**–**3** with some aromatic compounds are described.

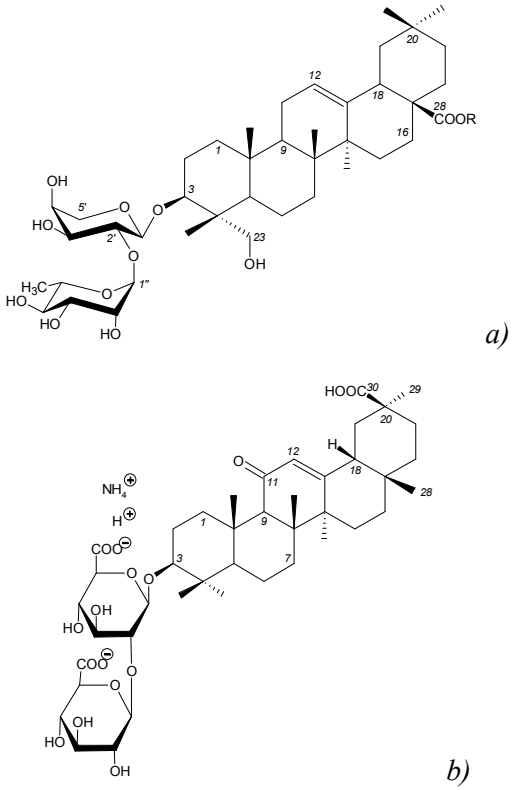

Fig. 1. Chemical structures of ivy saponins (*a*) (**1**: R=H; **2**: R=←βGlc$_p$-(6←1)-βGlc$_p$-(4←1)-αRha$_p$) and monoammonium glycyrrhizate (glycyrram) (*b*).

Complexes with caffeine

Caffeine (1,3,7-trimethylxanthine) is one of the most important alkaloids. It is found in coffee beans, cocoa beans, cola nuts, guarana and bottle tree seeds, tea leaves, and Paraguay tea [17–20]. The caffeine content of tea can reach 5 %, and in the seeds of guarana, more

than 6 %. It stimulates the central nervous system, reduces the effects of sleeping pills and drugs, has diuretic properties, and enhances cardiac function [13, 17]. Herbicidal [21], antifungal [22, 23], and molluscicidal properties have also been found [24–26].

Recently, hetero association of caffeine with various substances has been extensively studied [27]. The molecular complexes of caffeine were obtained with glycosides **1** [28] and **2** [29]. UV spectroscopy confirmed that intermolecular interactions exist between glycosides and caffeine. As the glycosides **1** and **2** concentration increases at constant caffeine concentration ($0.50 \cdot 10^{-4}$ M), the optical density of their solutions increases (hyperchromic effect). The absorption maximum of the solutions decreases insignificantly (hypsochromic shift) from 272 to 265 нм for glycoside **1** [28], and from 272 to 270 nm for glycoside **2** [29].

The complexes composition was defined by the method of isomolar series and of molar ratios (saturation method) [30]. It was established that glycosides **1** and **2** form complexes with caffeine in a 2:1 molar ratio. The same ratio was found for molecular complexes of glycyrrhizic acid and some drugs [1, 2].

It was supposed that the complexation leads to disruption the self-association of caffeine. Clathrate complex between glycosides and caffeine formed by hydrophobic interactions of the glycosides aglycon (hederagenin) with the heterocyclic system and methyls of caffeine. The formation of intermolecular *H*-bonds involving the pyrimidine C=O and the imidazole *N*-atom of caffeine and the OH groups of the glycosides monosaccharide units was also possible.

It was shown by electrospray-ionization mass spectrometry that trimers and hexamers of caffeine can not occupy the space formed by two molecules of glycosides **1** and **2**, and complexation does not occur in this case [31].

The spectral data indicating that intermolecular interactions occurred between caffeine and the glycoside in aqueous solution were also confirmed by studying the biological activity. The toxicity of glycoside **1**, caffeine, and their complex for mollusks *Planorbis corneus* (Planorbidae) and of glycoside **2**, caffeine, and their complex for fish *Poecilia reticulata* (Poeciliidae) was studied [28, 29]. The complex of glycoside **1** turned to be less toxic with the pure glycoside and more toxic than caffeine. The biological activity of caffeine complexed with glycoside **2** was reduced.

The effect of triterpene glycosides **1** and **2** in their complexes with caffeine on the electrical activity of the grape snail visceral ganglion non-identified neurons was studied [32]. The complexes activated electrophysiological neurons rate, and they had an opposite kinetics of entering and outgoing currents. Thus, while glycoside **1** complex activity the entering currents were increasing and the outgoing ones decreased, and while using glycoside **2** complex both entering and outgoing transmembranous ionic currents decreased. Previously it was found that bidesmosidic triterpene glycosides do not effect on the neurons background activity [33, 34]. Thus, complexation with caffeine activates neurotropic effect of bidesmosidic glycoside **2**.

Complexes with sildenafil

Today sildenafil citrate (fig. 2) is one of the most widespread drugs for treating erectile-dysfunction (viagra, intagra ic, novagra, erectile, etc.) [35] and pulmonary

hypertension (revatio) [36]. sildenafil citrate is an ingibitor of phosphodiesterase-5 (pde-5) [35].

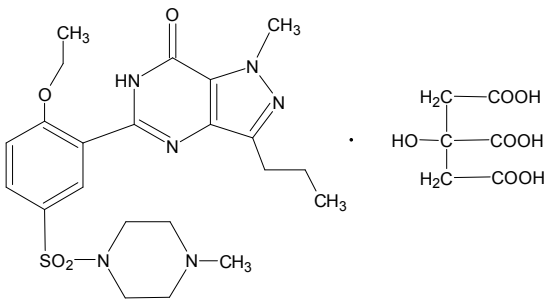

Fig. 2. Chemical structure of sildenafil citrate.

Molecular complex of glycoside **1** with sildenafil (in the basic form) was prepared [37]. The result of intermolecular interaction in the IR spectrum of complex is the shift of absorption line of glycoside **1** and sildenafil CO-group. In the complex spectrum analysis the decrement of valence oscillations frequencies of OH- and NH-groups, the increasement of amide line II frequency and change of $\nu_{as}(SO)$ and $\nu_{s}(SO)$ absorption frequencies were observed. This indicates the possible association of molecules at the expense of intermolecular *H*-bonds formation occurring through glycoside OH-groups, and sildenafil NH- and SO-groups as well.

Using a method UV-spectroscopy, the molecular complexation of sildenafil citrate with glycosides **1** and **2** in aqueous [38] and aqueous-alcoholic solutions was investigated [39]. It was found that the glycosides form complexes with sildenafil citrate in the 1:1 molar ratio. Intermolecular interaction has been accompanied by a hyperchromic effect. IR-spectroscopy confirmed that intermolecular interactions exist between saponins and sildenafil citrate [38].

The ichtyotoxic activity of the supramolecular complexes **1** and **2** with sildenafil citrate was investigated on *Poecilia reticulate* (Poeciliidae) [38]. Comparative study of influence of glycosides and complexes on seeds germination *Avena sativa* L. has been made [39].

With the help of intracellular diversion the effect of sildenafil citrate and its complexes with glycosides **1** and **2** on electrical activity non-identificated neurons of *Helix albescens* Rossm. visceral ganglion was examined [40]. Opposite neurotropic effects of sildenafil citrate and its complexes were demonstrated. Sildenafil citrate application resulted in neurons activation, while glycoside complex on neurons soma provoked their activity depression.

Previously it was shown that bidesmosidic triterpene glycosides did not effect on neurons electrical potentials [33, 34]. However, it is proved that sildenafil citrate binding to bidesmosidic glycoside **2** results in development of neurotropic effects manifesting in changes of neurons electrophysiological rate. This effect is not characteristic for the use of pure sildenafil citrate and glycoside **2** [40].

Using UV- and IR-spectroscopy, the molecular complexation of **3** with sildenafil citrate was investigated [41]. If concentration of **3** increases at constant sildenafil citrate concentration (10^{-4} M), the increasement of solutions optical density is observed (hyperchromic effect). The composition of the complex was determined by the method of isomolar series at absorption maximums of the **3** (258 nm) and sildenafil citrate (291 nm) [17]. This method gave a molar ratio ≈0.81 and ≈0.80, which corresponded to a 1:1 complex.

IR-spectroscopy indicates the possible association of molecules at the expense of intermolecular *H*-bonds formation occurring through compound **3** COOH and OH-groups, and sildenafil SO-groups as well. Compound **3** and sildenafil citrate are the salts, therefore between them ionic interactions are observed. As a result, the absorption frequency of CO in the communications group at the COO^- of **3** increases by 7 cm^{-1} and the sildenafil citrate – to 18 cm^{-1}.

CONCLUSIONS

1. The molecular complexes of **3** with sildenafil citrate, and triterpene glycosides **1** and **2** with sildenafil citrate and caffeine were prepared.
2. The composition of the complexes was determined by the method of isomolar series. The complexation is confirmed by UV- and IR-spectroscopy.
3. Influence of molecular complexes on parameters of the electrical activity of neurons, seeds germination, mollusks and fish was described.

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Яковишин Л.А. Молекулярное комплексообразование сапонинов плюща и солодки с некоторыми лекарственными веществами ароматической природы / Л.А. Яковишин, В.И. Гришковец, Д.Ю. Белаш, И.Р. Яровой // Ученые записки Таврического национального университета им. В.И. Вернадского. Серия «Биология, химия». – 2011. – Т. 24 (63), № 3. – С.4-10

Описано молекулярное комплексообразование моноаммонийной соли глицирризиновой кислоты (глицирама) с цитратом силденафила, а также 3-О-*α*-L-рамнопиранозил-(1→2)-О-*α*-L-арабинопиранозида хедерагенина (α-хедерина) и его 28-О-*α*-L-рамнопиранозил-(1→4)-О-*β*-D-глюкопиранозил-(1→6)-О-*β*-D-глюкопиранозилового эфира (хедерасапонина С) с цитратом силденафила и кофеином. Обсуждены вопросы определения состава комплексов, их биологической активности и межмолекулярных взаимодействий при комплексообразовании.

Ключевые слова: тритерпеновые гликозиды, α-хедерин, хедерасапонин С, моноаммонийная соль глицирризиновой кислоты (глицирам), цитрат силденафила, кофеин, супрамолекулярный комплекс, биологическая активность.

Яковішин Л.О. Молекулярне комплексоутворення сапонінів плюща і солодцю з деякими лікарськими речовинами ароматичної природи / Л.О. Яковішин, В.І. Гришковець, Д.Ю. Білаш, І.Р. Яровий // Вчені записки Таврійського національного університету ім.В.І. Вернадського. Серія „Біологія, хімія”. – 2011. – Т. 24 (63), № 3. – С. 4-10.

Описано молекулярне комплексоутворення моноамонійної солі гліцирризинової кислоти (гліцираму) з цитратом силденафілу, а також 3-*О*-α-*L*-рамнопіранозил-(1→2)-*О*-α-*L*-арабінопіранозиду хедерагеніну (α-хедерину) та його 28-*О*-α-*L*-рамнопіранозил-(1→4)-*О*-β-*D*-глюкопіранозил-(1→6)-*О*-β-*D*-глюкопіранозилового естеру (хедерасапоніну С) з цитратом силденафілу і кофеїном. Обговорено питання встановлення складу комплексів, їх біологічної активності та міжмолекулярних взаємодій під час комплексоутворення.

Ключові слова: тритерпенові глікозиди, α-хедерин, хедерасапонін С, моноамонійна сіль гліцирризинової кислоти (гліцирам), цитрат силденафілу, кофеїн, супрамолекулярний комплекс, біологічна активність.

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