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In long-term medication of patients, some medicinal preparations produce, along with a positive target action, side effects leading to undesired consequences. Among such effects we should primarily mention toxicity, which is characteristic of potent medicines applied in the chemotherapy of cancer and other severe diseases. Therefore, the search for low-toxic pharmacons with a high therapeutic activity remains vital. The essence of a new approach to the development of low-dose medicinal preparations based on the method of clathration (complex formation) of pharmacons with natural substances, glycosides, is presented. Medical compositions thus created contain an essentially lower therapeutic dose of an active substance, so they are less toxic and possess some new useful properties.

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On the Way to Low-Dose Medicines

T. G. Tolstikova, A. G. Tolstikov, and G. A. Tolstikov*

The development of medicinal preparations and their introduction into medical practice are long-term, interrelated, and complex processes. It often turns out that the more promising a preparation appears to be, the stronger (strange as it may seem) the impetus to perfect its properties. If we put aside such obvious reasons for this impetus as the desire to get rid of the harmful side effects of a preparation or (as with antibiotic and antiviral drugs) to break the resistance of microorganisms and viruses, quite an understandable and natural desire to improve the success achieved comes to the fore.

Two main approaches to upgrading the properties of medicinal preparations are clearly identified in contemporary medical chemistry. The first one, which is characterized by a careful attitude to the chemical structure of a "fortune preparation," proceeds from the fact that its insignificant alterations will result in some modified substances ("modificants") capable of manifesting the required activity in lower doses than the initial preparation does. In addition, there are hopes for the possible emergence of new useful properties in modificants, in particular, a substantial reduction in the toxic effect. The second approach does not suggest any changes in the chemical structure of a "fortune preparation." It is based on creating medicinal formulations, in the composition of which the pharmacon is protected from its untimely destruction by the living body's metabolic processes, as well as on acquiring increased transport capacities with more clearly expressed affinity to the active receptor centers.

In critically comparing both approaches, note that the first one, which has become widespread in recent decades, is successfully used for upgrading preparations of special social significance and high cost. These are often preparations synthesized from natural (vegetable, microbial, and animal) raw materials. For example, the base of paclitaxel, an antitumor preparation, is a taxol alkaloid, derived from the metabolite of 10-deacetylbaccatin, contained in the needles of the English yew, *Taxus baccata,* whose cost is more than $300 000 per 1 kg. Synthetic transformations of taxol that do not disturb the molecule's tetracyclic frame, the carrier of its basic pharmacological properties, may differ in the complexity of their modifying fragment's structure. In particular, the preparation taxoprexin (Fig. 1), now in its second phase of clinical trials, was obtained from a simple synthetic operation as the ether of taxol and polyenic acid. However, the synthesis of the preparation DJ-927, now being tested clinically, has required a more serious alteration of the taxol structure. Currently, we have promising results of clinical trials on ten new derivatives of taxol, while more than 20 derivatives are undergoing preclinical tests. This interest in taxol's structural modifications is rooted not in its high cost but in the uniqueness of its pharmacological activity, which has put it on top of a new class of cancerostatic drugs with an action mechanism related to control over the polymerization of tubuline.

The history of the development of antimalaria preparations is very instructive. According to statistics, malaria sufferers account for hundreds of millions, while around two billion are constantly in the risk zone. The situation is still more dramatic because of the emergence of more strains of the disease's agent, *Plasmodium falciparum*, which are resistant to well-proven preparations, such as quinine, chloroquine, and mefloquine. Considerable success has been achieved by

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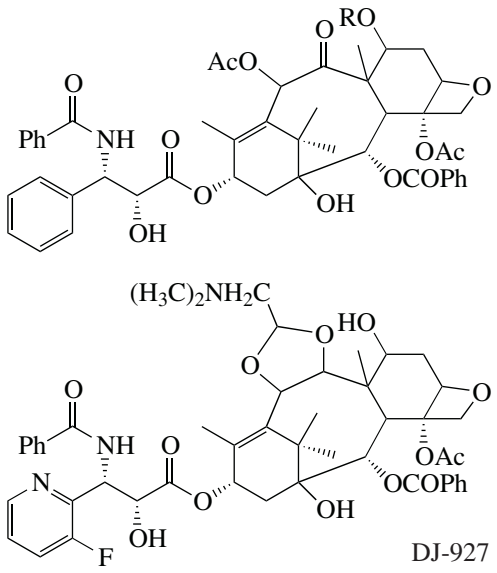

Fig. 1. Taxol (R=H) and its derivatives—taxoprexin (R = $COCH_2(CH_2CH{=}CH_8)C_2H_3$) and the preparation DJ-927.

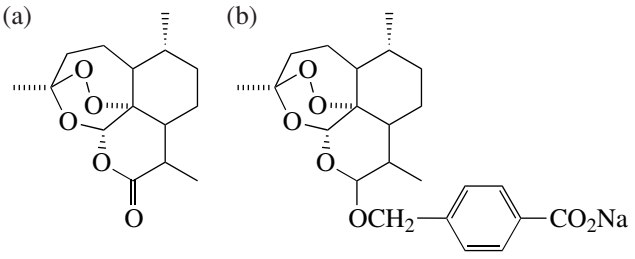

Fig. 2. Artemisinine (a) and its water-soluble derivative, artesunate (b).

China's government within the framework of the antimalaria program, which was announced at the end of the last century. Having studied the drugs of ancient medicine, described in the 3rd and 4th centuries AD, Chinese researchers found that sweet wormwood, *Artemisia annua L.*, which is widespread in Asia, generates a metabolite, which was later called artemisinin. This substance acts against any strains of malaria's agent. The mechanism of action, related to the presence of the peroxide (–O–O–) group in artemisinin's molecule, completely excludes any chance of resistance for the agent.

We can assess the special place artemisinin has taken in the line of antimalaria drugs by the fact that its production from wild wormwood in China and Vietnam has exceeded 10 t a year. The volume of storing and processing vegetable raw materials can easily be assessed by the content of the target compound in it at a level of 0.1–0.2% of dry weight. It is useful to note here that sweet wormwood was promptly introduced into US culture.

The industrially produced artemisinin is mainly used for obtaining synthetic modifications with increased water solubility and, as a result, higher activity. As in the case with taxol, the introduction of substituents that ensure water solubility does not disturb the basic frame of the artemisinin molecule (Fig. 2). Research related to artemisinin's synthetic modificants has gained a worldwide scale. Even the safe European countries appreciated the potential danger of the return of old times when malaria took away the health and lives of tens and hundreds of thousands of Europeans.

Despite the success of methods for upgrading medical preparations based on the first approach, we should assume that modificants are new preparations that need a complete cycle of pharmacological investigations. The attractiveness of the second approach is in using formulations of well-known and preparations with nontoxic substances that have been thoroughly tested clinically. The latter, which usually lack basic activity, serve to provide the pharmacon, through forming a complex with it, with protection from metabolism, better transport, and increased affinity to receptors. It is extremely important that the use of well-known substances makes it possible to reduce significantly the costs of preclinical tests and clinical trials of formulations.

According to the latest data, taxol complexes, as well as those of other costly plant cancerostatics with natural and synthetic polymers of hyaluronic and poly-L-glutaminic acids, polyacrylamides, polyvinylpyrrolydone, as well as with oligosaccharides, are undergoing thorough investigations. The most noteworthy of the latter is cyclodextrins (most frequently, β-cyclodextrin) and their derivatives with cationoid or anionoid groups. However, the practical realization of preparations containing cyclodextrins often provokes alarm owing to the certainly presented but incompletely studied toxic properties of these cyclooligosaccharides.

The root of glabrous and Uralian licorices (*Glycyrrhyza glabra L., Gl. uralensis*) belongs to the oldest medicinal drugs described in the chronicles. The root's main metabolite—triterpenic glycoside of glycyrrhyzic acid, the content of which in the raw material amounts to 25%—possesses remarkably diverse pharmacological activities that are matched by low toxicity. This explains the unquenchable interest of researchers display in its chemistry and pharmacology. Another important reason for this interest is the availability of glycyrrhyzic acid, which is determined by considerable licorice-root procurement. For example, in 1987, the Soviet Union, one of its leading suppliers to the world market, procured more than 20 000 t of the root [1].

Having studied the chemistry and pharmacology of glycyrrhyzic acid for some years, we have come to the conclusion that it belongs to a still small group of natural bioactive metabolites with a unique combination of properties [2]. As a typical (and, probably, outstanding) representative of this group of substances, glycyrrhyzic acid, on the one hand, has demonstrated rare respon-

siveness to the structural alterations, enabling us to derive modificants with a rich selection of pharmacological properties, and, on the other hand, has revealed itself as the complex former of pharmacons. Thus, this acid is nearly an ideal object for employing both approaches aimed to improve preparations' pharmacological properties.

With its antiviral activity, including the properties of the reproduction inhibitor of human immunodeficiency virus (HIV-1), human herpes viruses (HHV-6, HHV-7), and hepatitides B and C viruses, glycyrrhyzic acid has shown a high capacity to alter antiviral properties depending on the character of modifications. For example, introducing acyl substituents into hydroxyl groups of the carbohydrate part (Fig. 3, track A) allowed us to obtain new agents (we named one niglizin) that formed the first group of highly effective inhibitors of the reproduction of Marburg virus, which causes acute hemorrhagic fever in humans with a high mortality rate. Moreover, niglizin, with the same activity as azidothymidine towards HIV-1, is superior to the latter in its HIV-2 inhibition effect. A combination of niglizin with azidothymidine (AZT) is a promising drug against AZT-resistant HIV mutants. Niglizin is also active as a synergic component in compositions with nevirapine, a well-known anti-HIV preparation. Hence, the discussed modification of glycyrrhyzic acid produces agents with a potential for effective HIV-infection therapy [1, 3].

Modification of carboxyl groups (Fig. 3, track B) by additional carbohydrate fragments has led to inhibitors of the reproduction of the severe acute respiratory syndrome (SARS–CoV) viruses [3]. A line of other modifications of the glycyrrhyzic acid molecule's carboxyl group allowed us to obtain a new group of immunostimulants superior in their activity to the well-known preparation N-acetylmuramyldipeptide, as well as to reveal compounds with neuroleptic and antidepressant effects.

However, particularly interesting results have been obtained when, governed by the second approach principles, we used glycyrrhyzic acid as the complex former of pharmacons. While studying these properties of licorice glycoside, we quickly comprehended that the opening opportunities had outperformed our boldest expectations. Research into the pharmacological properties of pharmacons introduced into animal bodies along with glycyrrhyzic acid brought us to the conclusion about the emergence of in vivo complexes (clathrates) with different molecular correlations of components, which is determined by the optimum of the pharmacon's basic activity. Clathrates are primarily attractive in their basic activity in doses substantially (to 100 times) lower than the known therapeutic ones. In addition, in a number of cases, we registered the amplification of the pharmacon's secondary pharmacological properties, as well as the appearance of useful properties that were new for a given preparation. Thus,

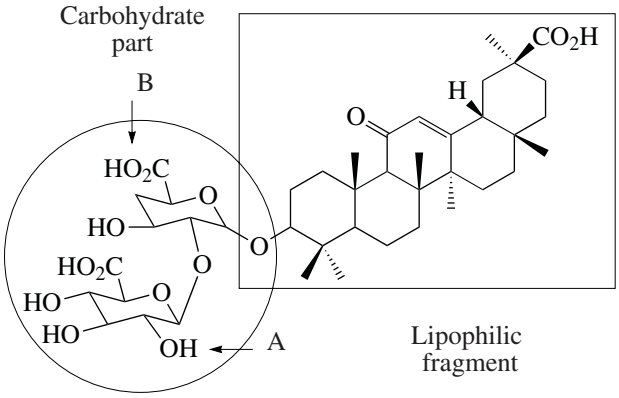

Fig. 3. The structure of glycyrrhyzic acid and the ways of its modification.
(A) Introduction of acyl substituents into hydroxyl groups, and (B) a modification of carboxyl groups.

we can say that glycyrrhyzic acid takes part in the formation in vivo of some specific supramolecular structures that act as independent and pharmacologically active agents, interacting with receptors by a specific mechanism.

We can characterize the makeup of these supramolecular structures in the following way. The molecule of glycyrrhyzic acid, like the molecules of other glycosides, consists of aglycon—a lipophilic fragment—and a carbohydrate chain—a hydrophilic fragment (see Fig. 3). The abundance of polar groups (OH, CO_2H) not only conditions the imperative of the molecules to self-association but also supports the stable bondage of pharmacons in aqueous solutions (consequently, in living organisms, too).

The study of aqueous solutions of glycyrrhyzic acid by the method of small-angle x-ray scattering has shown that, at a concentration of 1 mM, this acid forms associates in the form of rods with a radius of 14 Å and a length of up to 600 Å. The introduction of the pharmacon participating in complex formation with glycyrrhyzic acid causes the destruction of the associate and the formation of stable complexes. For example, according to the NMR-spectroscopy data, nifedipine, an antihypertensive preparation that has the basic (alkaline) nitrous fragment, forms a toroidal complex with glycyrrhyzic acid (GA), whose molecular composition is GA : pharmacon = 2 : 1. The stability of the complex is ensured by both hydrogen bonds, emerging inside the toroid between OH groups of the carbohydrate fragment of glycyrrhyzic acid and the polar NO_2 and CO_2CH_3 groups of the nifedipine molecule, and the acidi–base interaction of the glycoside's carboxyl groups and the nitrous fragment of nifedipine (Fig. 4).

As will be shown below, the maximal action efficacy of pharmacons linked to glycyrrhyzic acid falls upon the molecular ratios of GA : pharmacon = 4 : 1 and even 8 : 1. Probably, in solutions and in vivo, there may exist larger structures (clathrates), not only providing the

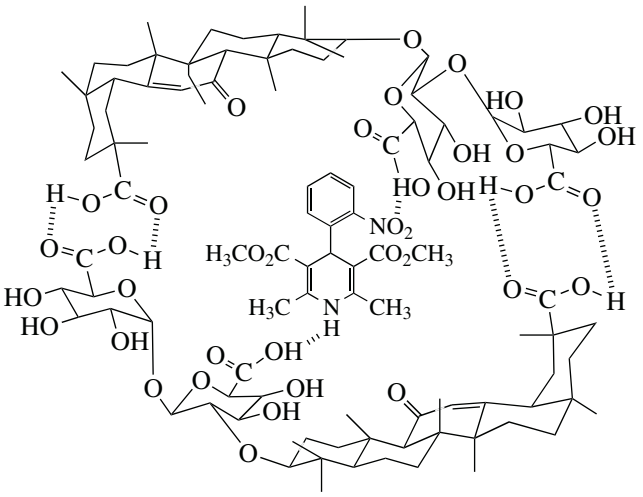

Fig. 4. The glycyrrhyzic acid–nifedipine complex with a molecular composition of 2 : 1.

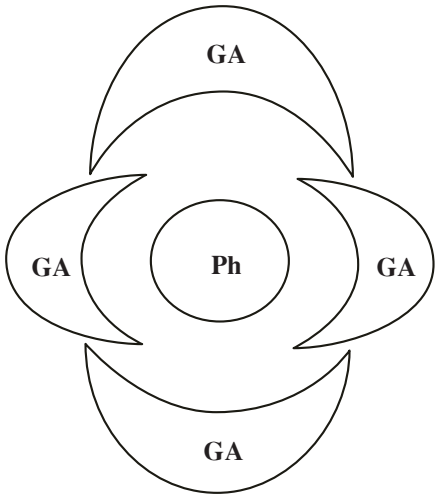

Fig. 5. The diagram of the glycyrrhyzic acid–pharmacon clathrate with a molecular composition of 4 : 1. (GA) glycyrrhyzic acid and (Ph) pharmacon.

optimal characteristics of the pharmacon's basic activity but also determining the emergence of new properties or the strengthening of pleiotropic properties.

Judging by the experiments' results, the effect produced by the complex-formation (clathration) with glycyrrhyzic acid spreads onto the pharmacological properties of preparations with a variety of actions. In particular, we have found this effect, which, in our opinion, is practically important, for complexes of glycyrrhyzic acid with well-known preparations of psychotropic (fluoxetine, phenibut), cardiotropic (nifedipine, allapinin), anti-inflammatory (acetylsalicylic acid, butadion, indometacin, ortophen, analgin), and luteolytic (prostaglandin, cloprostenol) action [1].

For better perception of the material, let us recall such characteristics of medical preparations as LD_{50}, ED_{50}, and ThIR. The value LD_{50}, or the mean lethal dose, is determined for all medical preparations, primarily on experimental animals, and characterizes the dose at which 50% of them die, in other words—the acute toxicity dose of a preparation. To assess the basic property of a medical preparation, the efficacy dose indicator (ED_{50}) was introduced, with which the 50%-effect of a medical preparation is achieved. The notion of the therapeutic index range (ThIR) is determined by the LD_{50}/ED_{50} ratio and characterizes the range of human safe doses of medical preparations. The larger the ThIR value, the safer the medicinal preparation is. Unfortunately, a lot of medical preparations widely used in contemporary medical practice are toxic and have a narrow range of the therapeutic index, which often prevents their long-term therapeutic use.

Note also that the approach being developed by this paper's authors, which suggests clathration of pharmacons by plant glycosides, aims at obtaining compositions with reduced doses and toxicity but with preserved high basic activity. One of the clathration results may be the strengthening of indirect pleiotropic properties of preparations. Let us consider some examples of clathration with glycyrrhyzic acid.

Clathration of psychotropic pharmacons. Molecular complexes and clathrates of glycyrrhyzic acid have been obtained with fluoxetine (FLX), an antidepressant, and phenibut, an anxiolytic, of different compositions. Their effect on the central nervous system was assessed on laboratory animals (mice) according to standard models. The effect was compared with model preparations, in this case, with fluoxetine and phenibut. The results of the screening performed on the tests "forced swimming" (antidepressive action) and chloralhydrate sleep (sedative action) and the 5-oxytryptophane test (action on serotonin receptors) have shown that the greatest activity is exercised by clathrates of the molecular composition GA : pharmacon = 4 : 1 (Fig. 5).

Full identity of the antidepressive action of the clathrate GA : FLX = 4 : 1 with the fluoxetine action has been shown in mice males of the C57BL/6J lines, using the social depression model. Here the pharmacon dose necessary for the manifestation of the required effect is reduced 17 times in the clathrate, while the toxic effect decreases 20 times (LD_{50} of the clathrate is >5000 mg/kg, and LD_{50} of fluoxetine, 248 mg/kg). The therapeutic index range also rises 20 times [4].

Phenibut is a nootropic and tranquilizing agent that lowers tension and anxiety and improves sleep. Its drawbacks include sleepiness and allergic responses. The clathrate of glycyrrhyzic acid with phenibut (4 : 1) revealed an effect analogous to the pharmacon's, but the dose was reduced 16 times. Compared with phenibut, the clathrate increases mnestic abilities (memorizing capacity) in animals and possesses a decreased sedative activity. Its toxicity decreases

1.7 times, while the therapeutic index range increases 17 times [1].

The clathration effect of cardiotropic preparations. We have performed a series of experiments for the clathrates of glycyrrhyzic acid with nifedipine, an antihypertensive preparation, and allapinin, an antiarrhythmic. The choice of these preparations can also be explained by the fact that both exhibit adverse and toxic effects. The preliminary experiments have shown that the clathrates of GA : pharmacon = 4 : 1 possess the optimal activity.

It has been established in an acute pharmacological experiment on the Wistar rats, as well as on those with genetically predetermined arterial hypertension (NISAG line), that nifedipine and its glycyrrhyzic-acid clathrate, containing a 10-times reduced dose of the pharmacon, lower blood pressure practically the same amount. It is noteworthy that glycyrrhyzic acid itself in the dose used has no hypotensive effect.

In studying the antiarrhythmic activity on the standard models of calcium-chloride and adrenaline arrhythmias, clathration has unexpectedly been found to enhance considerably this secondary effect of nifedipine. In the first model, the clathrate manifests a dose-dependent effect. Thus, the clathrate's dose of 0.120 mg/kg prevents the development of arrhythmia by 80% and blocks the already developed one by 90%. For a dose of 0.250 mg/kg, these indicators are respectively 100 and 90%. Since the absolute content of the pharmacon in these doses is 0.012 and 0.025 mg/kg, while nifedipine itself blocks the development of arrhythmia by 80% in a dose of at least 3.5 mg/kg, it is clear that, to arrest and prevent the development of calcium-chloride arrhythmia, the clathrate can contain nifedipine in a dose reduced 140 to 290 times [5]. Therefore, the glycoside clathration effect for nifedipine is manifested not only in a 10-time reduction of the therapeutic dose sufficient for its antihypertensive activity but also in its considerably enhanced secondary pharmacological property—antiarrhythmic effect.

The high-toxic (LD_{50} = 6 mg/kg at intravenous introduction) allapinin (lappaconitine hydrobromide, a diterpenic alkaloid) is on the clinical list of antiarrhythmic preparations. We obtained for the study a clathrate with the formulation GA : allapinin = 4 : 1, which we patented under the name of allaglyzin. The LD_{50} of intravenously introduced allaglyzin was found to be 12 times lower than that of allapinin. A comparative study of the antiarrhythmic activity of allapinin and allaglyzin administered parenterally to mongrel male rats produced the following results. As shown on the above two arrhythmia models, the therapeutically effective dose of allapinin within a complex with glycyrrhyzic acid decreases 14 times, and its toxicity, 12 times, while its therapeutic index range increases by 260 units [6].

The clathration effect for nonsteroid anti-inflammatory drugs. For experiments, complexes were obtained with nonsteroid anti-inflammatory drugs (NSAIDs), such as acetylsalicylic acid, ortophen, butadion, analgin, and indometacin, in ratios of GA : NSAID = 2 : 1. For these complexes, on six experimental models of acute and chronic inflammation, an anti-inflammatory, antipyretic, and analgesic activity has been established, which was three to five times higher than that of the initial NSAIDs and in essentially reduced doses (1.5–2 times). The acute toxicity of GA–NSAID complexes is reduced two to fourteen times, compared to the initial preparations. The complexes' ThIR is three to eleven times higher than that of basic NSAIDS. NSAID clathration diminishes two to five times the destructive lesions of stomachic mucosa (ulcerogenic effect).

These data allow us to hope for a real possibility to develop principally new preparations based on well-tested NSAIDS, which has no adverse toxic effects. This possibility is particularly true of the ulcerogenic effect that sharply narrows the NSAID applications [1].

Prostaglandins–glycyrrhyzic acid clathrates are a new class of uterotonic drugs. Prostaglandins, due to their power to stimulate the uterine muscles (uterotonic action) in ultra-low doses, have found wide application in medicine and veterinary practice. Cloprostenol—one of the main veterinary preparations—is produced, as other prostaglandins, through multistage synthesis. As a result, the high cost of preparations highlights the need to reduce the therapeutically active dose. In addition, it is necessary to raise the stability of labile prostaglandins in end products.

We have succeeded in solving both problems through clathrating prostaglandins with glycyrrhyzic acid [1]. We have obtained complexes of glycyrrhyzic acid with prostaglandins of the lines E (PGE_1, PGE_2, sulproston) and F ($PGF_{2\alpha}$ and cloprostenol). The study of the uterotonic properties of the complexes in the tests on the uteruses of rats and guinea pigs has led to the following results. The complexes GA : PGE_1 = 1 : 1 and GA : $PGF_{2\alpha}$ = 1 : 1 caused changes in the uterine contraction amplitude two times stronger than the preparation PGE_1, based on sodium salt. Sulproston– and PGF_2–glycyrrhyzic acid complexes (1 : 1) increase the uterine contraction amplitude three times compared to the basic prostaglandins. At the same time, the tonus of the uterus increased. The complexes, unlike the initial prostaglandins, are stable substances, and their solutions are storable at a room temperature for a long time. If necessary, the complexes can be pelletized. It should also be stressed that complex formation with glycyrrhyzic acid raises the water solubility of the initial prostaglandins, thus making preparations on their basis able to be administered intravenously. The principal result was a reduced dose of the costly prostaglandins with synchronous betterment of all the therapeutic parameters.

Based on the glycyrrhyzic acid–cloprostenol clathrate, a highly effective veterinary preparation, clathro-

prostin, has been developed, with the acting substance's dosage 5 times lower than that used worldwide. The preparation was produced by the pilot production facility of the Institute of Organic Chemistry (IOC), Bashkir Research Center, Ural Division of the USSR Academy of Sciences (now IOC, Urals Research Center, RAS) in cooperation with the Mechnikov Institute of Vaccines and Serums, Ufa. The output substantially met the demand of pig-farm complexes, veterinary needs, and the country's fur-animal-breeding industry. With a cost half the price of imported drugs, the effect of the preparation was essentially more physiological than that of the best imported preparations.

We have developed and patented the preparation clathiram, based on glycyrrhyzic acid and cloprostenol. With the prostaglandin (cloprostenol) dose reduced more than 20 times, the new preparation is a more efficient luteolytic drug to synchronize desire in cows than the well-known estrophan. Clathiram has a regulating effect on labor activity (synchronization of farrows in sows) with a 35-times lower prostaglandin content than in estrophan. The postpartum period in cows treated with clathiram decreases by 15 days compared to animals treated with estrophan. Clathiram is more effective than estrophan in the treatment of ovarian dysfunctions in cows during the transplantation of embryos. Treatment of acute and chronic endometria in cows is effective with clathiram doses three times lower than in the case of estrophan.

Can we extend the clathration effect to complexes of pharmacons with other glycosides?

Our experimental data allow us to answer this question positively. In our search for plant glycosides of substances capable to form complexes with pharmacons, we focused on requirements for them such as the potential availability and minimal toxicity. The choice of the next object of research into the clathration effect fell on acanthophylloside B. This triterpenic glycoside is contained in the root of a Central Asian plant, *Acanthophyllum gypsophyloides* [7]. The root itself ("soapy root") has been used since ancient times in Central Asia in halva-cooking. At present it is used in the food industry as an emulsifier. We have shown that acanthophylloside B forms clathrates with prostaglandins, which, similarly to the above described clathrates of prostaglandins with glycyrrhyzic acid, are strong uterotonic agents [1].

Diterpenic glycosides—stevioside and rebaudioside, produced by a tree plant, *Stevia rebaudiana*,—turned out to be highly effective clathrating agents. Both glycosides belong to the fourth class of low-toxic substances (stevioside's LD_{50} is 10 000 mg/kg, and rebaudioside's, 8 000 mg/kg). Stevioside is an industrially produced and widely used sweetener in the candy industry and winemaking. Undoubtedly, if necessary, the production of *Stevia rebaudiana* glycosides can be redistributed for pharmaceutical needs.

The series of experiments that we conducted with the stevioside complexes and clathrates with the pharmacons of cardiotropic and psychotropic action revealed some specific features of the clathration effect manifested under the action of stevioside. The complex stevioside : allapinin = 1 : 1 and the clathrate of the same molecular composition (4 : 1), preadministered to animals, provide complete protection against the development of both calcium-chloride and adrenaline arrhythmias. The effect of the two substances on the developed calcium-chloride arrhythmia is low. However, clathrate stevioside : allapinin = 8 : 1 unexpectedly manifested the power to protect animals completely not only by preadministration but also under a developed calcium-chloride arrhythmia. The fact of such an activity "surge" indicates a principal possibility for pharmacons to function as clathrates of a more complex structure than was shown above. Note that the allapinin content in clathrate compositions 4 : 1 and 8 : 1, which show basic therapeutic activity, is respectively reduced 12 and 16 times [18].

A comparative study of fluoxetine and its clathrate activity with stevioside (stevioside : pharmacon = 4 : 1) has revealed the unidirectionality of their antidepressive action. The clathrate's therapeutic effect is fully revealed even when its pharmacon's content is reduced 16 times. The toxicity of the clathrate is 32 times lower than that of fluoxetine.

The second glycoside of *Stevia rebaudiana* is rebaudioside, for which we have also revealed a moderate antiarrhythmic effect, which demonstrates a remarkable clathration effect. The basic hypotensive activity is reached in the clathrate rebaudioside : nifedipine = 4 : 1, with a 5-times reduced dose of the pharmacon.

Clathrate rebaudioside : nifedipine = 4 : 1, like the glycyrrhyzic acid–nifedipine clathrates, is able to arrest and prevent the development of calcium-chloride arrhythmia with the pharmacon's level reduced 200 times compared to the therapeutic dose [1]. Thus, the glycoside clathration effect is in principle extendable to pharmacons with a variety of actions, while the circle of clathrate-forming glycosides can be widened.

Summing up the discussed above, let us consider advantages that, as we think, can be obtained using the glycoside clathration effect. First, this is a reduction in the pharmacon's therapeutic dose:

Pharmacon	*Dose reduced, times*
Fluoxetine	17
Phenibut	16
Nifedipine:	
antihypertensive effect	10
antiarrhythmic effect	290
Allapinin	14
NSAID (mean value)	1.5–2
Cloprostenol	5–35

Second, it is a reduction in the toxic adverse effects specific for different groups of pharmacons. For example, antiarrhythmics of the allapinin type are known for their cumulation potential, which can lead to the reverse effect—a sudden development of arrhythmia and even a lethal outcome. Administration of allapinin as a clathrate with glycyrrhyzic acid will reduce the level of cumulation owing to both the reduced dose and this acid's hepato- and nephroprotective properties that help normalize the pharmacon's metabolism. It is suitable to mention here that glycyrrhyzic acid is a reliable source of glucuronic acid that can be used as a transport agent at the final stages of metabolism—the elimination of the pharmacon as its conjugates [1, 2].

Reducing a nifedipine dose in its clathrating with glycosides can assist in diminishing the risk of stenocardia progression and other cardiovascular complications. Moreover, the nephroprotective properties of glycyrrhyzic acid are able to prevent the development of renal deficiency in the treatment of various forms of arterial hypertension, particularly, renal. Noteworthy is the opportunity of using nifedipine clathrates in cutting short arrhythmia without affecting arterial blood pressure, since the pharmacon dose with anti-arrhythmic effect is 29 times lower than the antihypertensive dose.

As for the fluoxetine clathrates, there exists a real chance of reducing the level of drug dependency thanks to the strong antidote activity of glycyrrhyzic acid. The most valuable result of NSAID clathration with glycyrrhyzic acid is, undoubtedly, a reduction (essentially, two to five times) in their ulcerogenic effect. Moreover, the application of NSAIDs as clathrates will raise the protective functions of the liver and kidneys.

We cannot avoid stressing high prospects for the glycosides of *Stevia rebaudiana* as the potential components of low-dose medical preparations. These available plant metabolites deserve thorough study. The authors of this paper feel that the clathration of pharmacons with plant glycosides is an economical and prospective way to low-dose medical preparations.

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