KAPITEL 3 / *CHAPTER 3* [3]

THE ROLE OF GLUCURONIC ACID IN BIOTRANSFORMATION OF XENOBIOTICS: CHEMICAL ASPECTS

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Introduction

The human body has complex systems of metabolism and detoxification of dangerous compounds. These systems have undergone a long evolution under the influence of natural toxic components of food, water, air and various biological poisons. In the XXI century, the human body began to be exposed to various synthesized substances (xenobiotics). In connection with the negative trends in the dynamics of health of the population of Ukraine and the world, it is important to understand the processes of adaptation of the human body to the effects of chemical factors of anthropogenic origin and the search for factors of health restoration in the conditions of their constant exposure. According to modern ideas, the toxicity of chemical compounds of anthropogenic origin, some drugs and products of their metabolism for different people is manifested in different ways, but the metabolic processes are based on the same chemical transformations, that is, the schemes of biotransformation of xenobiotics and nutrients are similar. Intolerance of chemical compounds or tolerance of the human body to chemicals of anthropogenic or synthetic origin are determined by the genetic characteristics of each individual, so they are considered by individual clinical cases or scientific observations of certain groups of people and are selective. The generalization of information from biochemical, chemical, physiological and dietary sources is important for understanding the full picture of getting rid of toxicants from the human body and saturation with useful biologically active substances, with the possibility of increasing the degree of realization of their chemical potential. To do this, it is only necessary to create the proper conditions under which the processes of metabolism of foreign substances will become more or less controlled and predictable, and the metabolism of nutrients will proceed more fully [1].

It is known that most foreign substances (xenobiotics) when entering the body do not have a direct biological effect and are metabolized under the influence of human genetic polymorphism. The study of the main components of the enzymatic systems

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that ensure the implementation of xenobiotics metabolism allows to identify deviations in the process of detoxification of chemical compounds, which makes it possible to adjust the main links of the metabolic transformation of toxicants, and the enzymatic components of the detoxification system to be considered as markers of xenobiotic metabolism disorders caused by increased individual sensitivity and stable intake into the body from the environment.

The concept of biotransformation of xenobiotics covers not only enzymatic chemical transformations, but also transmembrane transfer, tissue distribution, deposition and elimination. In the course of biotransformation, two types of compounds can be formed: less hazardous than the original ones, and others with greater reactivity than the original ones. The high chemical activity of these compounds determines their ability to easily bind to biomolecules. This is the effect of the mechanism of toxic action.

When small amounts of xenobiotics enter the body, their detoxification is carried out in the usual ways - through enzymatic and non-enzymatic transformations. In the case of penetration of a large amount of foreign substances into the human body, these detoxification processes are not enough and superoxide anions, hydrogen peroxide, organic peroxides, etc. begin to accumulate in the body, which cause side effects of xenobiotics. Elimination of these effects is carried out with the participation of vitamins A, E, C, P, choline and amino acids (cysteine, methionine, arginine). Hence, it follows that the optimal functioning of the body's protective and adaptive systems against xenobiotics depends on its provision with complete proteins, trace elements (iron, selenium, copper), calcium, vitamins. Unfortunately, most groups of the population have an alimentary deficiency of the above nutrients, which requires priority correction of food rations in the direction of developing food components (functional foods or food additives to food) [2]. It should be noted that when consuming functional foods, excessive fats and carbohydrates can get into the body, and the consumption of food and dietary supplements is a worthwhile precaution for many people with metabolic syndrome (schoolchildren, young people, manual and mental workers working in state budgetary institutions of non-managerial format, pensioners, people with disabilities, etc.)

Therefore, it is relevant and important to search for opportunities to detoxify xenobiotics by typical compensatory-adaptive reactions that maintain homeostasis at the molecular level and do not affect the enzyme system, because with age, enzyme activity decreases and the amount of toxic substances increases.

Today it is recognized that glucuronic acid has a wide range of properties and physiological features aimed at detoxifying effect. We consider it important to study also natural substances, which include glucuronic acid: xanthan, glycyrrhizin, hyaluronic acid, in order to realize their physical and technological properties in the composition of composite hydrogels as the basis of a wide range of products for human health (food, pharmaceutical, medicinal, cosmetic products).

The aim is to model safe technological environments based on natural substances containing glucuronic acid (xanthan, glycyrrhizin, hyaluronic acid) in order to develop technologies of hydrogels with a wide range of useful properties for the human body.

3.1. Analysis of the chemical structure of glucuronic acid

Glucuronic acid is one of the uronic acids formed in the body from glucose during the oxidation of its primary alcohol group. Optically active, well soluble in water, tpl = 167...172 °C, monobasic. D-glucuronic acid is widespread in the animal and plant world, it is part of acidic mucopolysaccharides, some bacterial polysaccharides, triterpene saponins, hemicellulose and gum. In the form of paired compounds of glucuronic acid (glucuronides), some metabolic products, including poisonous ones (phenol, cresol), and many medicinal substances are excreted in the urine. The transformation of glucuronic acid in all animals, except for monkeys and guinea pigs, as well as humans, leads to the biosynthesis of ascorbic acid. The physiological fluids and tissues of animals (especially in the liver, kidneys, spleen, as well as malignant tumors), bacterial and plant tissues contain the enzyme β-glucuronidase, which catalyzes the hydrolysis of β-glucuronides into free glucuronic acid and the corresponding aglycone [3].

In fig. 1 shows the structural diagram of glucuronic acid, which clearly shows the number of functional groups, both for ionic bonding (-COOH) and for intermolecular interaction (-OH) with other participants of the technological environment and the gastrointestinal tract.

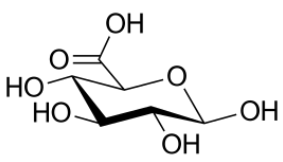

Figure 1 Structure of glucuronic acid

Glucuronic acid is found in small amounts in the human body, where it is formed during the oxidation of D-glucose. Its normal concentration in the blood is 0.02-0.08 mmol/l. Glucuronic acid is part of mucus, saliva, intercellular matrix, glycocalyx. It is one of the key components of pigment metabolism in the liver.

The properties of glucuronic acid to some extent coincide with the properties of glucose, but due to the presence of a carboxyl group, it is possible to create salts and lactones. When heated, glucuronic acid is dehydrated and decarboxylated.

An important function of glucuronic acid for the human body is that it is able to form soluble conjugates (glucuronides) with alcohols, phenols, carboxylic acids, thiols, amines and a number of other substances, due to which it is given the status of a powerful detox agent, which in addition, it faithfully removes the products of biotransformation from the body.

According to the opinion of a number of scientists, the biotransformation of xenobiotics in the human body proceeds in three phases.

In the first phase, as a result of the addition of new or the release of existing active functional groups (-OH, -SH, -NH3), the toxicant molecule is modified into a more polar and more hydrophilic compound than the original substance. Reactions of the first phase are provided by various enzyme systems localized mostly in liver cells [4]. Substances foreign to the body are activated with the help of cytochromes P-450 (family of cytochrome enzymes). Some other enzymes of the classes of oxidases, reductases and dehydrogenases can also participate in the first phase of biotransformation. The transformation of molecules in the first phase of biotransformation strengthens their polarity, reduces their ability to dissolve in lipids. Thanks to this alone, a number of foreign compounds are better excreted in the urine [5].

The second phase is the stage of biological conjugation of the starting substance and/or its intermediate products of metabolism with endogenous molecules, such as glucuronic acid, glutathione, sulfate, as a result of which polar compounds are formed, which are easily excreted by the kidneys or bile from the human body. In the process of the II phase of biotransformation, intermediate metabolites connect with endogenous ligands, increasing the hydrophilic nature of the compound, thereby promoting its elimination from the body. Some formed short-lived electrophilic metabolites have toxic properties. Enzymes involved in the second phase of biotransformation include N-acetyltransferase, glutathione-S-transferase, glucuronyltransferase, epoxide hydrolase and methyltransferase [6]. The reactions of the first and second phases are

catalyzed by enzymes known as xenobiotic-metabolizing enzymes. Most of these enzymes are concentrated in the liver, although activity is also manifested in other organs and tissues. As you can see, for the detoxification and elimination of xenobiotics, it is necessary to ensure a balance between the enzymes of the first and second phases. Thus, protect the body from damage that can be caused by the external effects of xenobiotics. Later, it was proved the existence of specific transfer substances of exogenous compounds – P-glycoproteins, which ensure the movement of xenobiotics in the body. Also, the main function of such transfer substances is to improve the process of excretion of xenobiotics (in bile or blood), which in some sources is called the third phase of biotransformation - the phase of evacuation.

Biotransformation, as a rule, leads to a decrease in the activity of toxicants - deactivation. However, in some cases, metabolites of xenobiotics become, on the contrary, more toxic compounds, and can also change the nature of the toxic effect or initiate another toxic process [7].

Glucuronide conjugates of xenobiotics have a 5-pyranoside structure and are classified as follows:

1) O-glucuronides are formed from phenols, alcohols and carboxylic acids;

2) There are several types of N-glucuronides. The nitrogen atom of these compounds, to which the glucuronide part is attached, can be in an amino, sulfamide, carbonyl group or in a heterocyclic nitrogenous compound.

3) S-glucuronides - thiol compounds with glucuronic acid [8].

A characteristic feature of glucuronides is that the carboxyl group in their molecules remains free. Therefore, in plasma and urine, glucuronides are almost completely ionized by the carboxyl group.

The general scheme of absorption of glucuronides is shown in Fig. 2.

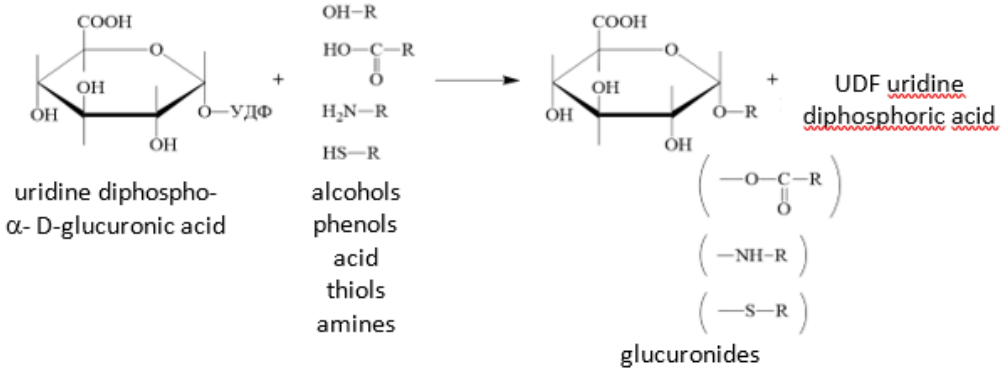

Figure 2 – The general scheme of absorption of glucuronides is shown in

Examples of types of glucuronide formation reactions are shown in fig. 3.

With the help of conjugation with glucuronic acid, some endogenous substances are also metabolized, for example, steroids and bilirubin [9].

In the intestines, under the influence of glucuronidase, an enzyme of the intestinal microflora, glucuronides can be split with the formation of substances capable of reabsorption and return to the blood (phenomenon of intestinal-hepatic circulation of xenobiotics).

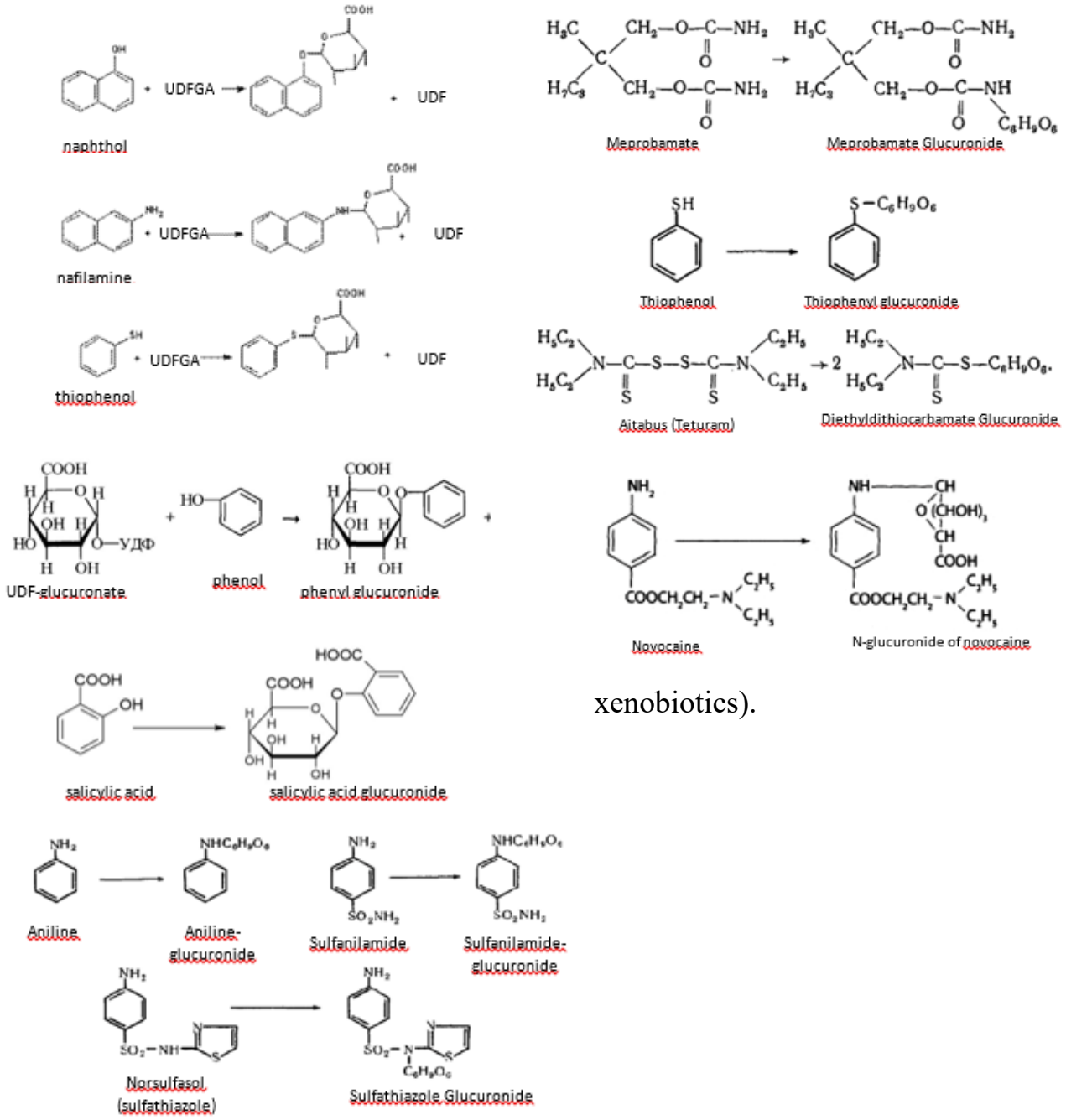

Figure 3 – Examples of xenobiotic glucuronide formation reactions

In a large number of publications devoted to the study of the metabolism of xenobiotics, the problem of identifying and using indicators that reflect the increased

sensitivity of an individual and identifying the main links of the metabolic transformation of toxic chemical compounds, the change of which can lead to a violation of the detoxification process in the body, is widely discussed.

The glucuronide detoxification pathway is one of the most loyal ways of removing toxins from the body. For its implementation, as can be seen from the table, it is necessary to involve the enzyme UDP-glucuronosyltransferase. Enzymes acetyl CoA, amine N-acetyltransferase, sulfotransferase, glutathione S-transferase, and cysteine-conjugating β-lyases are also involved in other ways.

In connection with the fact that there is a decrease in enzyme activity all over the world, that is, glucuronic acid is synthesized poorly in the human body, starting from the age of 25, it became necessary to search for external sources of glucuronic acid and study the mechanism of their assimilation in the human body. According to the results of the analytical review, glycyrrhizin, xanthan, and hyaluronic acid became such raw material sources.

3.2. Theoretical aspects of studying the properties of glucuronic acid in the composition of low- and high-molecular compounds

Glycyrrhizin (food additive E958) or glycyrrhizic acid (GA) is used as a sweetener and flavor and aroma enhancer. Glycyrrhizin is 50-100 times sweeter than sucrose. It is also used as a foaming agent in the production of halva. One of the most important derivatives of GA is its monoammonium salt (fig. 4).

In the structure of GA, a hydrophobic fragment corresponding to an aglycon residue and a hydrophilic part formed by a disaccharide fragment are distinguished. The presence of carboxyl groups in the aglycone ring and in the terminal residue of the disaccharide fragment of the carbohydrate chain determines the ability of GA to form various self-associates, which acquire stability due to the formation of hydrogen bonds [10].

In [11], quantum chemical calculations of the stability of self-associates consisting of 1-6 GA molecules were performed. The most energetically advantageous was the dimer built according to the "head to tail" type, which forms an internal cavity with a size of 0.65-1.47 nm. Among the larger GAn aggregates (n = 3-6), the "head-tail" type structures were also the most stable. They form a cavity about 1 nm in size. In addition, GA dimer and trimer ion peaks were found in the mass spectra (electrospray ionization).

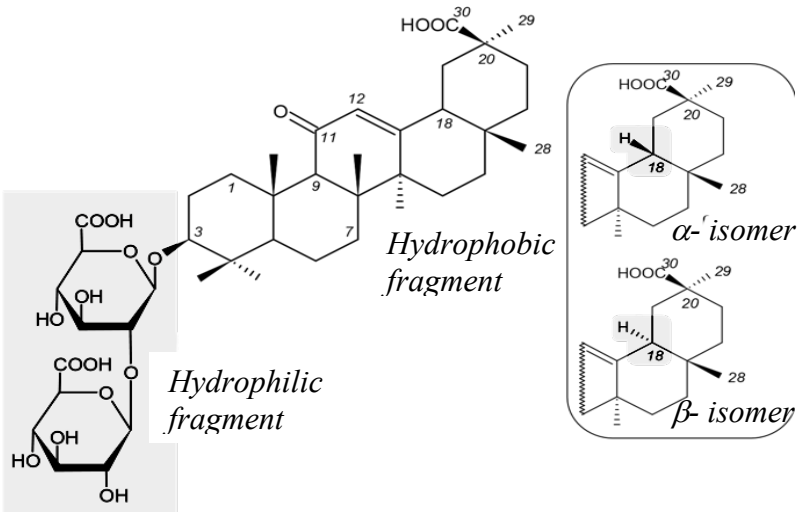

Figure 4 – Chemical structure of glycyrrhizin

It is known that xanthan is one of the most common polysaccharides in various fields of application. Xanthan is mainly used in the food and cosmetic industry as a thickener and gelling agent.

Hydrogels based on it are viscous solutions even at very low concentrations, and when the concentration increases, they turn into translucent amorphous substances. Glycosidic bonds in the structure of xanthan are hydrolyzed under the influence of acids and specific enzymes of the intestinal tract.

The unique biological and rheological properties of xanthan are largely determined by the ordered structure of its chains in solutions. Xanthan, as a high-molecular compound, has a primary, secondary and higher spatial structure. This is due to weak intramolecular interactions, among which hydrogen bonds and vander Waals forces play the main role (fig. 5).

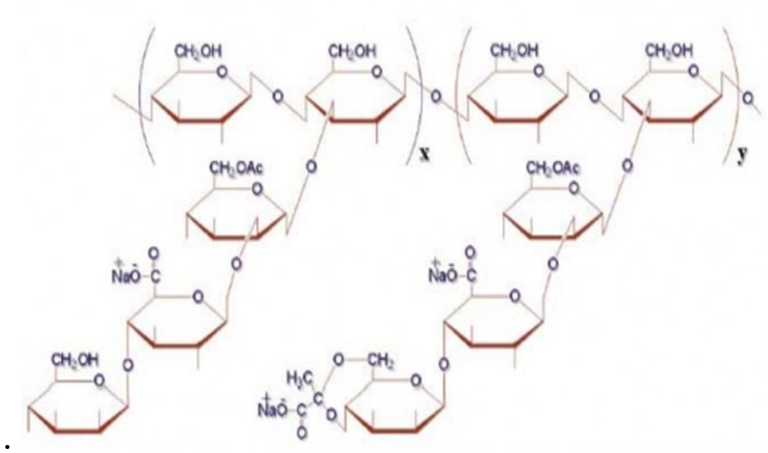

Figure 5 – Primary structure of the microbial exopolysaccharide xanthan

The main chain of xanthan is built similarly to cellulose (1-4-β-glycopyranose), and the side chain is presented in the form of a trisaccharide consisting of β-D-mannose, β-D-glucuronic acid and α-D-mannose. Residues of glucuronic acid and acidic pyruvic groups give xanthan molecules an anionic character.

As we can see from fig. 5, the spatial structure of xanthan hides part of the functional groups of glucuronic acid from interaction with xenobiotics/drugs/biologically active substances, so xanthan does not have a detox effect, at least in the stomach. When entering the gastrointestinal tract at a pH above 7, the tertiary structure of xanthan is destroyed, the side chains unfold, repelling from the main chain under the influence of the ionic strength of the solvent (water), and enable glucuronic acid to form a chemical bond with other substances. Such in the intestine are heavy metals, half-life products of macronutrients, radionuclides, toxins.

Hyaluronic acid is a non-sulfated glycosaminoglycan, an unbranched polysaccharide consisting of disaccharide units formed by N-acetyl-D-glucosamine and D-glucuronic acid, which are interconnected by β-1,3- and β-1,4-glycosidic bonds tongues (Fig. 6) [12]. The basis of sugar fragments is a glucopyranose ring with various substituted groups (acetamide, hydroxyl and carboxyl).

In the intestines, under the influence of glucuronidase, an enzyme of the intestinal microflora, glucuronides can be split with the formation of substances capable of reabsorption and return to the blood (phenomenon of intestinal-hepatic circulation of xenobiotics).

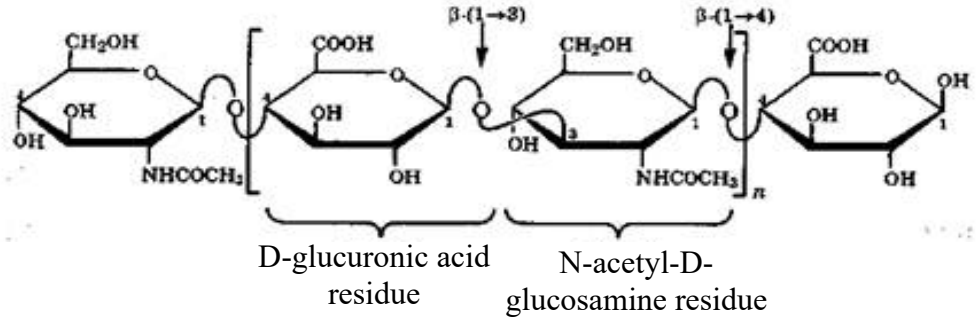

Figure 6 – Chemical structure of hyaluronic acid

Hyaluronic acid molecules are characterized by the formation of a large number of hydrogen bonds, both within the molecule and between neighboring carbohydrate residues that are distant from each other, and in aqueous solution even between closely spaced molecules through the carboxyl and acetamide groups.

Conclusion

From the above information, it is quite reliable that in the form of composite hydrogels based on xanthan, glycyrrhizin and hyaluronic acid, glucuronic acid realizes its unique detox properties in a wide range of technologies related to human health. In this regard, it is necessary to detail the picture of the formation of "niches" in order to further predict the beneficial properties of products based on composite hydrogels and control the processes of metabolism of xenobiotics. For this purpose, quantum chemical modeling of structural components can be proposed.