PART V

Eleutherococcus and Adaptogens: Generalizations and Hypotheses

ELEUTHEROCOCCUS: APPLICATION AND THE MECHANISM OF ACTION

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1. BASIC TRENDS IN ELEUTHEROCOCCUS APPLICATION

Modern civilization makes high demands of the physical and mental abilities of man.

Man's activity over the past 50-70 years have resulted in the pollution of our planet with industrial wastes. The number and variety of foreign chemical compounds (drugs, food additives, narcotics, dopes, etc.) purposely administered to man have drastically increased. In cities where the majority of the population of developed countries live, the diversity and power of man-made environmental factors (noise, vibration, radiowaves, etc.) are constantly increasing.

These additional chemical and physical loads adversely affected modern man who was unprepared for such stresses by the course of evolution. In addition, modern society places significantly greater mental demands on human beings, and new occupations appeared that require greater physical stress. Man masters the frozen waste of the Far North, makes himself at home in the Antarctic, conquers outer space, and makes plans to settle the depths of the ocean.

Current space, aviation and other special engineering, adapting the newest achievements of human thought, also makes unusually high demands of man.

Man's biological characteristics more and more hamper human activity. The gap between the rapid development of civilization and man's natural abilities grows continually. Man may be regarded as a peculiar chemical "machine". Is it possible to improve the performance of this "machine" in conditions that interfere with its operation by introduced externally chemical agents? Is man capable of playing the role of creator of his own chemical biological evolution? Can man increase his biological resistance and meet the demands made on him by the times? All these questions may be answered positively.

One of the most promising approaches to the problem of increasing man's non-specific resistance to damaging man-made factors and illnesses is the increase of individual resistance by pharmacological remedies that are classified in Soviet scientific literature as "adaptogens". This group includes extracts obtained from different plants (ginseng, eleutherococcus, aralia, schizandra, *Rhodiola rosea*, etc.), preparations of animal origin (pantocirne, rantorine, etc.), a number of synthietic drugs (e.g. benzimidazole derivatives), certain organosilicon compounds, the derivatives of aroxyacetic acid, and so on. We shall consider only adaptogens obtained from plants, many of which belong to the *Aralia* family.

According to the reported data (Dardymov, 1976), the active principle of these plants are glycosides. They act as drugs, which increase general non-specific resistance of the body, namely, resistance to diverse chemical, physical, and biological factors. Such drugs should be non-toxic and able to normalize deviations from the norm (Brekhman, 1968).

Eleutherococcus is undoubtedly the most remarkable and leading agent among these drugs. It is marked by a broad action range and low toxicity. In the USSR, there are rich natural resources of this plant. Eleutherococcus was tried in a large contingent of normal and sick persons. More that 1000 works are devoted to the results of its application, the mechanism of action and investigation of its active principle.

The greatest contributions to introduction of eleutherococcus to Soviet medicine and to medicine of many foreign countries have been made by Professor I.I. Brekhman and his scientific school. Numerous research works of this scientific school have demonstrated that eleutherococcus stimulates working capacity of animals and man, has a beneficial effect on intellectual activity, visual and auditory acuity in man. Eleutherococcus increases the resistance of animals and man to various injurious physical, chemical and biological factors (cooling, over heating, overloads in a centrifuge, action of narcotics and some antineoplastic agents and certain substances employed in industry and possessing toxic effects, exposure to some pathogenic microorganisms and viruses, etc.). The appropriate data are widely discussed in monographs (Brekhman, 1963; 1974; 1976; Dardymov, 1976; Li, 1981), and in a review by Barenboim and Kozlova presented in this collection.

Of great interest is an antimutagenic action of eleutherocccus extract with respect, in particular, to some antineoplastic drugs- mutagens. This action has been discovered in experiments on Drosophila by T.A. Sakharova jointly with Yu. A. Revazova and us.

The ability of eleutherococcus extract to potentiate antitumor immunity has been discovered recently. The laboratory headed by Prof. B.B.Fuka, Institute of Human Morphology, Academy of Medical Sciences of the USSR, in collaboration with our laboratory has revealed an increase in the membranotoxic (up to 200%) and cytostatic (up to 180%) activity of a group of antineoplastic lymphocytes- natural killers (NK) under the effect of eleutherococcus. The toxic function of the cancerous cell did not increase. Activation of NK was observed in the presence of a marked mutogenic effect of eleutherococcus in splenocytes and induction of the synthesis of y-interferon by leukocytes. Glycosides which are largely responsible for NK activation have been isolated. It is known that stress decreases the activity of the immune system, particularly that of NK. The effects described expand our knowledge of the antistressor action of eleutherococcus.

Despite such an abundance of works it is rather difficult to summarize and compare all the findings obtained by different authors. This is primarily linked with the fact that methods of qualitative and quantitative analysis of the active principle contained by eleutherococcus extract were not available until recently. The absence of the reference drug in experiments entailed fairly different and even contradictory assessments of the drug action. Moreover, most works, even when they are concerned with the same load on the body or the same damaging factor, commonly use different load doses, different animals and different experimental techniques. Therefore we consider the article by Kaplan and coworkers to be of paramount importance, since the authors performed experiments on animals using numerous exposure types and applied the same batch of eleutherococcus extract.

This together with its safety and its ability to increase the resistance of the normal human body to extremal conditions, make it the drug of social importance. Eleutherococcus and analogous drugs might be regarded as substances that would have been developed by nature in the human should the rate of evolution be comparable with the growth of the adverse effects of civilization on the human body. And it is exactly these properties of eleutherococcus that made it possible to test this drug on many healthy people in conditions of heavy physical work, intense psychological loads, and adverse climatic conditions. Certain results of these large-scale experiments involving thousands of normal subjects engaged in industry are discussed in the article by Barenboin and Kozlova.
These data show that the most popular drugs, eleutherococcus and dibazol, were applied on a city large scale (the population treated with dibazol amounted to 300,000), As a rule, the results were favourable and sometimes very noticeable (e.g. manpower losses decreased from 286 to 7 days per 100 workers at the expense of eleutherococcus intake at one of the shops of the Volga Automobile Plant).

Eleutheroccocus holds great promise for animal and poultry breeding. Intensification of agriculture at the expense of application of new equipment has given rise to untoward reactions among animals: new illnesses have appeared and productivity and fertility are being reduced. In this case too adaptogens are used successfully among which eleutherococcus most efficacious (Lyapustina, 1980).

Preliminary investigations of the action of eleutherococcus on simple embryonal models and experiments on animals have demonstrated that in certain cases individual eleutherosides B, D and E have a favourable effect on the resistance of sexual cells and embryos to external factors. Proceeding from these data the program has been formulated of the use of the adaptogens, including eleutherococcus, to increase the resistance of sexual cells and embryos in various conditions (see the article by Barenboim and Protozanova). Eleutherococcus and similar drugs may form strategic reserves for man's health in the near future. Even today the adaptogens may favour more harmonious relations between man and environment (complex and heavy work and unfavourable climatic conditions).

2. THE PRINCIPLES OF RESEARCH

Drugs similar to eleutherococcus can play the decisive role in the victory of man in a relentless struggle over his limited biological possibilities. Therefore, of great help would be the comprehensive knowledge of the mechanism of action of such drugs. What underlies the mystery of eleutherococcus action?

Different assumptions were advanced about the mechanism of eleutherococcus action at varying times. It was suggested that the main action of eleutherococcus reduced to its ability to inhibit free radicals formed mainly as a result of lipid peroxidation. Subject to discussion was the action of eleutherococcus on hexokinase, one of the key enzymes in energy metabolism. It has been reported that the action of eleutherococcus is accounted for by its ability to stimulate the biosynthesis of DNA, RNA and protein. A hypothesis of an insulin-like action of the extract was also put forward (Brekhman, 1968; Dardymov, 1976).

The hypothesis of the energy action of eleutherococcus extract has been developed in detail, according to which the mechanism of action of eleutherococcus glycosides may lie in their ability to control the energy and plastic supply of body functions by activating energy metabolism and stimulating biosynthesis of proteins and nucleic acids (Dardymov, 1976; see also the article of the same author in this collection).

According to this concept, eleutherococcus entails in the body the formation of a rapid and wise equilibrium between energy expenditures directly for functional processes and biosynthesis (based on the criteria of the maximal body viability). Of key importance is activation of energy supply to the importance is activation of energy supply to the organism's specific defense reactions at the cost of the regulation of functioning of the main enzymatic systems as well as stimulation of their biosynthesis.

Numerous hypotheses commonly attest to the lack of a sole reliable conception. This situation is lack of a sole reliable conception. This situation is typical not only of eleutherococcus. The molecular mechanism of ginseng action has been studied to a lesser degree, which according to written evidence, has been applied for about four thousand years. The mechanism of action of numerous drugs of the plant origin used nowadays in medicine has not been established as yet. As for many chemical preparations, the situation is the same, e.g. the first concepts of the molecular basis of the action of one of the most commonly used drug, acetylsalicylic acid, have been formed only recently. Therefore, as compared to many other drugs, eleutherococcus may be classified with the most investigated remedies. Nevertheless, the drug which may become a pharmacological health regulator for tens of million of people should be examined more thoroughly, and our understanding of its action should be comparable with what we know about the action of many antibiotics.

What would be the strategy of such a detailed study of the molecular mechanism of action of eleutherococcus, a multi-component drug whose pharmacological activity has been investigated completely enough?

The first stage is isolation of the components of the active principle and determination of their elementary composition and structural formula.

The second stage involves the design of the three-dimensional structures of the components of the active principle, calculation of the properties of its electron structure: determination of the types of interactions to which these structures are potentially capable, theoretical prediction of potential receptors.

The third stage involves study of the physicochemical properties of these components and the drug on the whole in order to predict its behavior in the body. Knowledge of these properties makes it possible to elaborate methods of quantitative and qualitative analysis of these components in the initial raw material, in the extract, and directly during industrial manufacturing, on storage and in experiments *in vitro, in vivo* and *in situ.*

The fourth stage is pharmacokinetic studies of the integral organism, organs, tissues and cells, including subcellular structures, in order to establish the possible sites of drug localization.

The fifth stage is a theoretical one (generalization of the concepts of the physico-chemical properties of the components and data on their localization in the body and pharmacological manifestations of their action). It involves the design of a draft hypothesis, their realization, assertion of the final concept playing the leading part at least until the new findings will make it necessary to revise all the previous hypotheses and the concept on the whole.

3. ELEUTHEROCOCCUS GLYCOSIDES: PHYSICO-CHEMICAL ASPECTS OF BIOLOGICAL ACTION

The works of the first stage involved isolation of the glycoside fraction from methanol extract of eleutherococcus. The fraction contained 7 glycosides called glycosides A, B, B_1, C, D, E, F. Later minor glycosides B_9, B_2, B_4 and others were discovered. The ratio of A: B: B_1: C: D: E: F is proved to be equal to 8: 30:10: 12: 24: 2: 1 (Ovodov et al., 1966; 1967; Suprunov and Dzizenko, 1970; Frolova et al., 1971: Frolova and Ovodov, 1971: Dardymov, 1976).

The chemical structure was defined for some of the above glycosides, including that for A, B, B_1, C, D (E). The biological action of these glycosides has also been studied more comprehensively.

The structural formulas of these eleutherosides taken from the literature, the electron structure and conformation of these molecules obtained for the first time by computation are presented in the article by Shamovsky et al.

Previously Ovodov et al, (1967) noted a certain similarity between the structural formulas of eleutherosides B and D and assumed that eleutherosides D and E are dimers of eleutheroside B. Detailed examination of the dimerization reaction made by Shamovsky et al. (1982) at our laboratory confirms the existence of these two reaction products. Obviosly in this case we deal with a sem-product and the end product of the synthesis performed by the plant itself (see also the article of these authors in this collection).

In our opinion, of great importance is the fact that the chemical structure of drugs with adaptogenic action obtained from natural sources (eleutherococcus, ginseng, schizandra, aralia, *Rhodiola rosea*, etc.) are represented by glycosides. Now let us consider how the physico-chemical properties of glycosides may affect their biological activity.

The presence of sugars in the structure of medicinal glycosides may obviously result in the following effects:

a) an increase of the solubility in aqueous phase of cells and tissues:
b) transfer of a glycoside via the cell membrane according to the mechanism of the transfer of individual sugars:
c) shielding of charges and hydrophobic areas of aglycone which reduces the probability of side interactions in the pathway of the glycoside to the target:
d) the presence of a definite address label on the glycoside molecule, which is detected by sugar as well as aglycone:
e) a possibility to transfer trace elements from the environment to the cell at the expense of the formation of complexes of cells and glycosides:
f) effect of a sugar residue on aglycone electron structure.

Below we consider some of the above-indicated items more comprehensively.

3.1 Solubility

Sugar residue that provides for a definite hydrophily of eleutherococcus glycosides ensures their solubility in water and in the blood and urine. Eleutherocccus glycosides (possibly, with the exception of eleutheroside A) can be readily absorbed by blood and occur here in a free state: they can be readily accumulated by tissues and organs, and be filtered unimpeded via the renal system, etc. As for eleutherodside V, this finding is confirmed, in fact, by data provided in this collection, (joint studies performed by the laboratories headed by Prof. I. N. Todorov and Prof I.I. Brekhaman and ours).

3.2 Permeability

Glycosides A, B, B_1, D (E) contain D-glucose, whereas glycoside C D-galactose. It is known that for these sugars there exists specifiic systems of active transport of sugars. All the eleutherosides may be absorbed by the cell or, at least, by the cell membrane by means of active glucose and galactose carriers.

The data in favour of such an assumption for eleutheroside B were obtained in our laboratory by N.N. Polukhina in experiments with red cell ghosts.

In principle, the assumption about active transport of glycosides can be checked up by recording eleutheroside penetration to the cell (according to the radioactive label or fluorescence) under the action on the cell of the inhibitors of the system of active sugar transport. Floridizine and mercurous chloride or p-chloromercuribenzoate may also inhibit glycoside transport. Their action on the system of aactive transport of sugars is prevented by thiols, which makes it possible to have a double control in experiments, as it were.

It is known that cell permeability for sugars is linked with the permeability of K and Na ions. In view of this, it is reasonable to perform experiments for measuring cell permeability for K* and Na* ions in the presence of individual eleutherosides.

3.3 Shielding

A shielding action of sugar residue on the charged atoms of aglycone and its hydrophobic part has been demonstrated with reference to the glycoside antibiotic olivomyein in experiments made at our laboratory (Pitina et al., 1981a, 1981b).

Unlike olivomyein, one glucose in eleutherosides B and B_1 and two glucoses in eleutherosides D and E are located so that shielding of even the nearest methyl groups is practically impossible. This follows from the spatial structure of eleutherosides, which is presented in the already mentioned article by Shamovsky and co-workers. Nevertheless, this problem is also discussed here, since such a situation is likely to occur for ginseng glycosides.

3.4 Recognition

Recently much attention has been given to the concepts that sugar residues of complex molecules serve, in many cases, as the structural basis of the intermolecular recognition. It is known that carbohydrates play the key role in intercellular interactions, in the interactions of some toxins with the cells, in the interaction of red cells with membranes of the hemopoietic and excretory organs, plasma membranes with different hormones, etc. (Vidershain, 1979: Bochkov et al., 1980).

As a rule, the steric principles dominate in this recognition: high flexibility of the o-glycoside bond between aglycone and sugar, flexibility of the bonds between monosaccharides, as well as the diversity of the monosaccharides themselves, make it possible to have a set of different conformations and provide broad possibilities of stereospeific recognition. In our laboratory I.L. Shamovsky et al. (1983) demonstrated, for instance, that conformational ability of carbohydrate components of cardiac glycosides plays the key role in the interaction between receptor and sugar, thus making essential contributions to receptor—aglycone interactions.

Three varieties of the eleutheroside address to the site of receptor meeting can be considered purely hypothetically:

- the address label is sugar: in this case aglycone that interacts with the receptor is transported;
- the address label is aglycone: sugar that is used in the system of sugar utilization is transported but aglycone ensures highly specific supply to the definite organs, tissues and cells:
- the address labels are sugar and aglycone: one label provides for a remote address (“country, city”), whereas the other one for a near address (“street, house, name”).

Address labels may provide for a definite spatial localization of glycoside in subcellular components. For example, and active carrier “pulls” glycoside A by glucose into the cell, whereas aglycone keeps by its cyclic part and a large hydrophobic “tail”, to the lipid part of the membrane. There occurs a definite spatial localization of glycoside in the membrane.

While treating sugar as and address label, it is necessary to bear in mind that glycoside is likely to break down at the expense of enzymes capable of sugar splitting. In this case the address label ceases its existence as such from a definite moment. It is important whether this will occur before or after the delivery to the site.

Splitting of the carbohydrate part from glycoside may also testify to a possible utilization of this group as energy substrate. Unfortunately, no chromatographic control was performed for the integrity of the structure of eleutheroside eliminated from the body (the article by Bezdetko et al. Presented in theis collection). Since this work has demonstrated that the radioactive label is localized on the aglycone, the fact of the presence of the radioactive label at the outlet does not prove either the presence or the absence of sugar in the end product, which is eliminated from the body. This problem requires further investigation.

3.5 Transfer of Trace Elements

Some eleutherosides are potentially capable of forming complexes with trace elements, particularly with metal ions. It may be assumed that in this case unusual “forceps” are formed from the sugar residue and aglycone, which “clamp” metal ion. The ability of glycosides to form such complexes has been studied by our laboratory with reference to the glycoside antibiotic olivomycin (Pitina et al., 1981a).

It is also of importance to examine in subsequent investigations the role of eleutherosides as a means for trace elements transport taking into account the most important role many trace elements in eleutherococcus extract performed by A. Ribokas and by us shows that it contains the most essential trace elements, such as calcium, phosphorus, potassium, magnesium, sodium, aluminum, barium, iron, strontium, boron, copper, zink, manganese, chromium and cobalt.

According to the preliminary data obtained by ouor laboratory jointly with the Irkutsk Institute of Organic Chemisty (Siberian Division, USSR Academy of Sciences), eleutherococcus extract contains germanium whose role in the living cells has been recently studied in different countries.

It may be assumed that some eleutherosides contained in eleutherococcus extract are basically related to certain trace elements present in the extract, transfer them to the living cells and deliver them to the necessary address determined by glycoside sugar residue or aglycone, on the one hand, and cellular receptor, on the other. On binding metals already present in the cell eleutherosides can control their catalytic action or activity as cofactors of a lot of enzymes.

3.6 Features of Phenolic Glycosides

After eleutheroside with or without a trace element gets to the receptor according to the address determined by sugar residue or aglycone they have to interact. What are the physico-chemical features of such an interaction?

Hydrophobic interaction at the expense of aglycone is possible. The data obtained by Shamovsky and his co-workers indicate that some of carbon atoms of aglycone, primarily those where the index of free valence is maximal, are likely to participate in reactions of radical addition. Aglycone may also form hydrogen bonds at the expense of the charged oxygen atoms.

In our opinion, the most important feature of phenolic glycosides obtained from eleutherococcus, related to their biological activity, consists in their potential ability to transform to different phenol derivatives (during enzymatic cleavage of sugar or methoxyl groups) including pyrocatechol derivatives (followed by formation of O-semiquinone) and pyrogallol, which are characterized by the ability for reversible oxidation, involvement in the different redox reactions of the cell, and high antioxidant activity.

Sugar bonded to aglycone by a flexible glycoside bond is not a ballast addition with regard to aglycone: its presence has a noticeable effect on the electron structure of aglycone, which is as if shadowed by glucose (Shamovsky et al., 1982,b).

In various reactions of eleutheroside glucose with cell components, changes in the sugar part can lead to changes in aglycone: sugar may play the role of specific regulator of the chemical behavior of aglycone.

4. ELEUTHEROCOCCUS GLYCOSIDES: THE PHARMACOKINETICS OF ELEUTHEROSIDE B AND SOME HYPOTHESES ABOUT ITS MECHANISM OF ACTION

The pharmacokinetics of many drugs, which are complex multi-component extract from natural objects, has not been studied so far. Eleutherococcus also falls into this category.

In 1979 the distribution kinetics of eleutheroside B_1 which was pre-labeled with tritium was first established (Bezdetko et al., 1981, 1982; German et al., 1982, and other articles included in this collection). These works are concerned with studies of the accumulation and elimination of eleutheroside B from the animal body, its distribution in individual organs and subcellular fractions. The highest level of incorporation was observed in the liver, kidneys and pancreas. Subsequently eleutheroside B is rapidly eliminated from these organs. The pituitary, heart muscle and adrenals show a tendency to drug accumulation between 2 and 4 hours after administration. In the testicles, thymus and brain, the label incorporation is insignificant and radioactivity drops to the minimal level by 75min.

Study of the content of ^{2}H-eleutheroside B in subcellular fractions has demonstrated that eleutheroside B is not accumulated in mitochondria of the organs under study. It could not be detected in liver nuclei either. The pancreas manifested an intense hiphasic accumulation of the label in the nuclei. In all the organs, the label was accumulated by microsomes, the rate of label accumulation in adrenal microsomes being 3-fold higher than that in microsomes of other organs.

It may be assumed that eleutheroside B stimulates or inhibits insulin synthesis in the cell muclei of the pancreas. To prove this hypothesis, one should study the relationship between the content of eleutheroside B and insulin amount in the body. It is also of importance to demonstrate that eleutheroside is found in the cell nuclei of Langerhans islets which are responsible for insulin synthesis in the pancreas.

The insulin-like action of eleutherococcus, which is analyzed in detail in the monograph by Dardymov (1876), provides evidence in favour of the assumption about the relationship between pharmacological activity of eleutheroside B and insulin action.

It has been shown in this collection that eleutherococcus extracts attenuated alloxan diabetes in animals. In certain cases these extracts serves as a good medicinal remedy for alloxan diabetes of medium severity in animals and mild forms of diabetes mellitus in humans. Similar effect was obtained in animal experiments with the use of sum total of eleutherosides.

These data and the pharmacokinetic findings allow the conclusion about the enhanced synthesis of insulin under the action of eleutheroside B. However, no data on this question are available in the literature.

The fact that eleutheroside B was found in the cell nuclei of the pancreas can be interpreted in a different way. Studies have revealed that eleutherococcus protects the islet apparatus of the pancreas from alloxan-induced injury (Dardymov, 1976). It may be assumed that eleutheroside B increases resistance and viability of the cells thus raising their efficacy without exerting any direct effect on insulin synthesis.

Let us discuss the accumulation of eleutheroside B in microsomes. Two assumptions can be at least made about possible functions of this compound in microsomes:

1) eleutheroside B is ballast material which undergoes chemical processing in microsomes:
2) eleutheroside B is a stimulant or inhibitor of microsomes.

It may be assumed that in the first case aglycone undergoes hydroxylation in microsomes. Particularly, it is exactly this process that may occur in microsomes of the adrenals, which are especially rich in hydroxylases. They may give rise to transformation of aglycone containing methyl groups so that both groups [$-OCH_3$], bonded to the aromatic ring of eleutheroside B are converted to [$-OCH_2OH$] groups.

Hydroxylation of eleutheroside B may compete with other main process occurring in the adrenals, i.e. with oxidation of different intermediate products of steroid hormones metabolism.

The article by Kovalev and Malenkov (1980) treates in detail a case when foreign chemical compounds (xenobiotics) affect the level of internal metabolism by competing with the products of the body itself in microsomes, particularly in the hydroxylation chain containing cytochrome P-450. If the enzyme effects hydroxylation of eleutherside B, then its presence will affect metabolism of steroid hormones.

It is tempting in the second case to view eleutherosides as inductors of monooxygenase containing cytochrome P-450. Such induction can proceed either via an increase in the synthesis of monooxygenase (as is the case with monooxygenase induction by phenobartial) or according to the feedback mechanism by which the biosynthesis is inhibited at the first stage (see the article by S.T. Sizova et al. in this book). In principle, phenolic glycosides are likely to be involved in the redox reactions of monooxygenase, which leads to activation of monooxygenase. The role of eleutherosides as potential stimulants of monooxygenase is in a good agreement with their protective importance in the body exposed in different xenobiotics and with the antistressor effects which can be linked partially with transformation to the water-soluble form and rapid elimination of endogenous steroidal structures.

Study of the mechanism of action of eleutherosides, even if their destiny has been accurately defined, does not shed light on the action of eleutherococcus extract on the whole. We can assume that the action of eleutherococcus is not a simple sum total of actions of all its constituent eleutherosides.

Eleutherococcus is probably a systemic drug. This term should be applied to the drug consisting of several chemically different components, each of which has its own site of application in the body and its own function, but the whole combination of these functions forms a definite system.

To illustrate this notion, let us imagine a certain non-existent systemic drug consisting of four components. The first component, for example, increases the content of any hormone that stimulates energy production in the cell: the second one increases synthesis of substances necessary for energy complex in the cell: the third one is conducive to sending this energy to the required channel: and the fourth one favours elimination of the hormone that had performed its tasks. Such a systemic pattern of active components of medicinal eleutherococcus extract could have been produced by the plant itself during evolution, which will be discussed more comprehensively in the concluding section of this article.

It is evident that in order to find the pharmacokinetics of eleutherococcus it is necessary to study the parmacokinetics of the remaining eleutherosides and to examine their combinations in pairs and in a complex.

Investigation of the pharmacokinetics of individual eleutherosides according to the radioactive label requires that each individual substance should be labeled or a culture of the eleutherococcus root should be grown, supplementing the medium with ^{14}C-compounds and then isolating eleutherosides, which may appear labeled. Eleutherosides B, B_1, D and E can be detected by fluorescence directly in the cells and tissues (the fluorescent properties are discussed in the article by Barenboim, Brikenstein et al., the appropriate methods of fluorescent microscopy are described in the articles by Barenboim et al. (1982), Morozova et al. (1982).

5. THE HYPOTHESIS OF THE EVOLUTIONARY ROLE OF ADAPTOGENS

What is the role of eleutherosides in the plant itself? What do panoxasides do in ginseng? What work is done by schizandra glycosides in the plant cells? These questions are not merely a matter of our curiosity. The living world is unique in its many manifestations. For example, deoxyribonucleic acid (DNA) acts as a carrier of genetic information in all the objects of the living world without exception—from virus to man. Adenosine triphosphoric acid serves as the energy keeper in all living cells: chromosomes, ribosomes mitochondria and many other structures of the living cell are organized in the same way. Such a unity of the main manifestations of life fives hope that having understood the functions of medicinal glycosides in the plant itself, we shall manage to comprehend much better their role in human organism.

Unfortunately these simple considerations are inapplicable to this case. The role of eleutherosides in eleutherococcus itself as well as the role of other medicinal glycosides in plants containing them have not been defined. This gives a right to extimate hypothetically their role in plants.

It is known that the *Aralia* family is not less than 150 million years. These plants are relict ones. They had grown on the Earth long before the appearance of man, namely during the period when the Earth was inhabited by giant dinosaurs (Vakar, 1973). The zone of their prevalence from the North spread to the tropics and included the entire present Far East of the USSR. The *Aralia* plants are detectable in the Cretaceous deposits on the island of Sakhalin and in some other regions of the Far East (Vassilvev, 1958).

During the existence of the *Aralia* plants, the Earth was repeatedly flooded by glaciers. During glacier invasions, the glacier did not descend below the 60th parallel and eastwards moved as far as Khaianga (the region of the peninsula of Taimyr). However, dramatic changes in the climate affected all the geographical regions of the Earth where the Far East, Korea, the northern part of China, Canada are found now (Monin, Shishkov, 1979). Some representatives of the Aralia family appeared in the ice age affected zone.

The exposure to severe climatic conditions and selection progressively distinguished those *Aralia* plants, which showed the occurrence of a definite complex of substances favouring the increasing of the plant resistance. These substances constituted the unique complex which was detected today in ginseng, eleutherococcus and other representatives of the *Aralia* family. It is this complex that plays an essential part in pharmacology.

This biochemical complex formed under the action of definite climatic conditions. That is why the representative of the *Aralia* family that did not fall into the ice age affected zone. Such a set of properties and did not become medicinal plants of the same value as the legendary ginseng.

After the glacier invasion had ended and the climate became far milder these properties of the increased resistance made ginseng have definite advantages over other plants. They include the possession of a mobile complex of protective means with regard to extremal factors of the environment.

Where did these substances come from? Did they exist long before the climatic trials that were undergone by the Aralia family or was it a consequence of the genetic changes that occurred at that period, leading to the appearance of a new trait?

It may be assumed that in the vegetable kingdom these substances also occurred in the plants belonging to the *Aralia* family long before the described events.

It is known that glycosides are widely spread among plants. In particular, in this form these occur different terpenoids (saponins, "cardiac" glycosides, steroid alkaloids, etc.). After enzymatic, non-enzymatic or photochemical degradation numerous foreign compounds are transferred in the plants to the glycoside form (libbert, 1976).

Eleutheroside B which is a monoglucoside of 4-β-glycoside sinape alcohol was discovered in the bark of lilac, whereas eleutheroside C (ethyl-a-D-ga-lactoside) was isolated from the seeds of lupus (I.V. Dardymov, 1976). These examples illustrate the prevalence of such substances in the plant kingdom. Selection but increased their number and formed such a kit of components, which favored the increase in the plant resistance.

It seems possible to regard the pharmacologically active substances obtained from Aralia plants as phytohormones.

According to the definition, phytohormones are chemical factors that are produced in a negligible amount in one part of the plant, transported to the other part where being in such an insignificant amount they are likely to display a regulatory action on the growth and development (Libbert, 1976).

Today three classes of hormones are known. They primarily act as stimulants (auxins, gibberellins, cytokinins).

Gibberellins, in particular, belong to the same class of terpenoids as ginseng panoxazides and eleutheroside A. Gibberellins occur in the plants in the form of free diterpenoids and in the form of glycosides.

If the mentioned phytohormones are primarily the hormones regulating the growth and development of the plants, the glycosides obtained from the *Aralia* plants and used in medicine as adaptogens may be called phytohormones of adaptation. Their hypothetical function lies in the increasing of the resistance and adaptation potentialities of the plants at the expense of the stimulation of energy processes and processes of biosynthesis that are important for ensuring the resistance of the plants. The action of such phytohormones responsible for adaptation is effected directly via the genome or by direct influence on the stimulated processes.

The glycoside form promotes rapid transport of adaptation hormones among all the parts of the plant. Such a system may be very roughly compare to the system of hormones involved in stressor reactions of man. It may be assumed by analogy that the plants have the phytohormonal system of their own that provides plant protection under stress. This system produced as a result of long-term exposures to environmental factors also plays an antistressor role in comparatively short-term exposures without losing its adaptation importance.

Thus, according to the suggested hypothesis a definite kit of eleutherococcus glycosides is a complex of chemical compounds, which ensure the increased resistance of the body to extremal factors of the environment.

During evolution of the living world this primary defense mechanism was apparently replaced in man by a complex system of the regulated homeostasis which in turn includes the systems of ionic and temperature stabilization, the immune system and the system of the stressor reactions.

The use of eleutherococcus extract or similar agents of modern pharmacology might be regarded in the light of this hypothesis as man's appeal for help to the nature, the return to the sources of his biological history. This is an appeal to the most ancient form of protection, which is provoked by the aggressiveness of the modern and future civilizations with regard to the body of man.

The facts presented in this section concerning eleutherococcus and ginseng are, in our opinion, a case of a more general hypothesis whose essence consists in the following.

Endogenous chemical compounds with a specialized function responsible for the resistance of the body to extremal factors of the environment exist in all the living organisms. The class of such substances that increase the resistance of the body may be conventionally called resistens. This class may be mostly found in the organisms which are incapable dramatically change their ecological niche (to rapid migration from the zone of action of extremal factors) like plants, some marine invertebrates and which are unable either to react to extremal factors by rapid genetic changeability as is the case with bacteria which are marked during adaptation to the environment by the predominate of factors of mutation, selection and accumulation of the mass of the most adapted cells.

The complex of resistens should be contained in all plant organisms. In the most complete form, the should be contained in those that either underwent long-term inhibitory effects of external extremal factors in the course of evolution or exist under extremal conditions of the environment today (the inhabitants of hot and cold sources, the plants living under acidic or alkaline conditions, under high saltiness, etc.).

According to this concept, the adaptogens obtained from the Aralia plants is a private case of such resistens. Glycosides form, in our opinion, the structural basis of resistens. Their biological activity determined by their physico-chemical structure is responsible for their broad potentialities which have been considered in the third section of this article.

The confirmation or rejection of this hypothetical conception will provide new data about this drug, the use of which and the like drugs is of paramount importance for establishing the harmony between the modern man and the environment, for the struggle with adverse sequels of the civilization, for the matter of the overall improving of the health of all the people living on the Earth. Such an approach has been considered by L.A. Piruzyan, A.G. Malenkov and G.M. Barenboim in an article concerned with the chemical activities of the humanity and protection of the environment (1979).

Thus, there has emerged one more role of eleutherococcus as an original center around, which there crystallize new concepts and hypotheses having the general biological value.

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