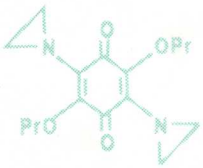
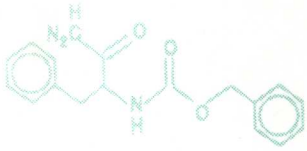


BIOACTIVE COMPOUNDS:

BIOTRANSFORMATION AND BIOLOGICAL ACTION



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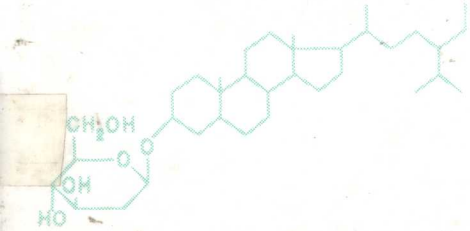

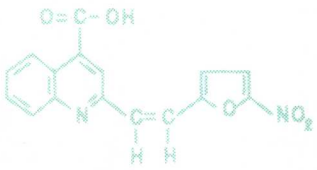

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I.N. Todorov, G.E. Zaikov,
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PREFACE

Advances made in chemotherapy are due to the operation of mechanisms of drug action at molecular and cellular levels. Biotransformation is one of the most significant aspects of mechanisms of drug action, it involves any drug-induced alterations occurring in organisms, cells, and model systems, including enzymatic transformations, namely metabolism, as well as spontaneous chemical reactions which are not mediated by enzymes. Biotransformation may result in activation or inactivation of different systems. In both cases, biotransformation may lead to an increase or decrease in therapeutic and/or adverse effects. In this context a search for ways of influencing or regulating the drug biotransformation seems to be essential.

The book includes a number of reviews covering the studies biotransformation of different classes of synthetic, natural, and endogenous compounds. Special attention is given, where possible, to the biological consequences of biotransformation reactions and to the possibility to affect biotransformation by showing more favorable pharmacological effects.

The choice of subjects of the analysis is due to the interest shown by the authors of the present manuscript and reflected the directions of investigations made in the Department of Kinetics of Chemical and Biological Processes, Institute of Chemical Physics, Russian Academy of Sciences.

A major portion of the drugs considered here have been synthesized, tested or approved for use in Russia and we would like to attract the attention of a wider range of researchers and investigators to the study and application of the compounds in question.

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THE KEY ROLE OF BIOGENESIS MODULATION OF CORTICOSTERIODS

I.N. Todorov

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"Such agents as ginseng (Panax) and Elutherococcus have recently aroused a great interest especially in RUSSIA. Many known clinical and experimental studies suggest that these agents produce nonspecific antistress effects. Further studies are, however, required before these assumptions receive greater recognition."

H. Selye. In: The new aspects in hormones and mechanism of their action.—Kiev: Naukova Dumka, 1977, p. 50.

INTRODUCTION

Search for an effective substitute of ginseng (Panax ginseng C.A. Mey), a celebrated medicinal agent of the ancient east, led to studies of the plants most related to ginseng among those of the same genus Araliaceae. The comparative examinations of ginseng and other Araliaceae types, which were initiated by I.I. Brekhman and his pupils as early as the mid-1950's at the Department of Pharmacology, the Far East Research Center, USSR Academy of Sciences, indicated that Eleutherococcus senticosus Maxim was the most promising substitute for ginseng. The findings that Eleutherococcus has the pharmacological potency comparable to that of ginseng as shown by some tests stimulated active studies of the action of Eleutherococcus extract and its components on the human and animal body not only in Russia, but in other countries as well. Enormous natural reserves of the plant available in the Far East, Russia, Sakhalin, Korea, Japan, and some Chinese provinces are also an important factor that contributes to the general interest in Eleutherococcus as a drug. Moreover, studies of cultured Eleutherococcus demonstrated that the plant can be grown from seeds and grafts. Eleutherococcus grows much faster than ginseng and it is more adaptable to the environment.

Great interest in this plant-derived agent was expressed at the First International Symposium on Eleutherococcus (Hamburg, 1980) and the Second International Symposium on Eleutherococcus (Moscow, 1984). These symposia

were attended by Soviet investigators together with those from the USA, the UK, Bulgaria, India, Switzerland, Sweden, FRG, Yugoslavia, Korea, and Japan.

It is widely believed that Eleutherococcus belongs to a group of drugs by the general name "adaptogens." N.R. Faransworth et al. [1], Health Research Center, University of Chicago, believe that adaptogens should have three pronounced properties. The first property of an adaptogen is lack of toxicity. Eleutherococcus extracts were tested in many animal species and it was shown that the lethal dose of a dried extract given per dose was over 30 g/kg. Numerous investigations (more than 6,000 observations) of the effects of the Eleutherococcus extracts on human activity have been conducted. None of them has revealed any significant toxic effects of the agent. The second aspect of adaptogens is their nonspecific action. The ability of Eleutherococcus to artificially simulate stress under various stress conditions (heat, cold, excessive exercise, hypokinesis, etc.) and its favorable effect on various human functions (visual acuity, color differentiation, hearing, fatigability, thinking in association with motor activity, etc.) indicate a wide range of unspecific action of the drug. The third property of an adaptogen is its capacity of displaying a normalizing effect regardless of physiological abnormalities caused by damaging influences (e.g., normalization of blood pressure in patients with both elevated or lowered pressure or normalization of blood sugar levels in hyper- or hypoglycemia following Eleutherococcus treatment).

The evidence for the adaptogenic nature of Eleutherococcus extracts is vast, however, the mechanism of its adaptogenic action requires further studies. In the past 30 years, some 1,500 papers dealing with various directions in Eleutherococcus investigations have been published mainly in Russia. A wealth of knowledge of various aspects in the action of Eleutherococcus on the human body stimulated its application in medicine. The credit for introducing Eleutherococcus as an adaptogen into medical practice is given to Prof. I. Brekhman and his school [2–6].

Since the main purpose of our paper is to review the results of the studies of the mechanism of biological action of Eleutherococcus extracts and its basic active components, glycosides (or "eleutherosides" as generally called in special literature), we shall briefly outline the data on 1) chemical and physicochemical properties of eleutherosides and some of their pharmacological properties, including those on higher biological resistance of man and animals under unfavorable environmental factors, 2) on the use of the drug in preventive and clinical medicine, 3) on a wide adaptogenic spectrum of Eleutherococcus, mainly its protective properties under deteriorating ecological factors, etc., as there are detailed reviews made by I. Brekhman [5,6], I. Dardymov [7], G. Barenboim and N. Kozlova [8]. Primary emphasis will be focussed on reviewing the data on the biological activity of Eleutherococcus and its glycosides; on its total anabolic effect; impact on protein and nucleic acid biosynthesis, immunogenesis; effects on interferon biosynthesis, carbohydrate and lipid metabolism; antistress action, etc. The paper will present the complete results from a series of studies made at the

laboratory of Molecular Biology, Institute of Chemical Physics, Russian Academy of Sciences, under the guidance of the author of the present review. The studies were undertaken to examine the pharmacokinetics of eleutheroside B (the major Eleutherococcus glycoside) and the mechanism of antistress and anabolic actions of the eleutheroside and Eleutherococcus extracts on higher animals.

1. CHEMICAL AND PHYSICOCHEMICAL PROPERTIES OF ELEUTHEROCOCCUS

1.1. Chemical Composition of Eleutherococcus Extracts. Structure of Eleutherosides

A glycoside fraction was isolated from the methanol extract of the eleutherococcus root, which displayed 7 glycosides designated as eleutherosides A, B, B_1, C, D, E, and F. The eleutherosides are in a ratio of 8:30:10:12:24:2:1. Later minor glycosides B_2, B_3, B_4 and others were detected. In addition to eleutheroside, the Eleutherococcus contains glucose, saccharose, starch, polysaccharides, pectin and many other compounds [7,9–15]. The majority of Eleutherococcus glycosides were isolated as crystals, which enabled the determination of their chemical structure (Figure 1). The first group (eleutherosides B, B_1, D, E) includes glycosides having genins of an aromatic nature. Eleutheroside B was identified with syringin and represents a monoglucoside of 4-β-glucoside of sinapis alcohol.

B_1 is a 7-α-glucoside of isofraxidine. Its aglycone is a 6-,7-,8-trioxycoumarin derivative, eleutherosides D and E are syringaresinole diglucosides, they vary in solubility in water and organic solvents and they seem to have a slightly different configuration. Figure 1 shows that eleutherosides D and E are close in structure. Eleutheroside D is known to represent a eleutheroside B dimer. This is like to apply to eleutheroside E. The scheme given below, illustrates the process of eleutheroside B dimerization:

I.L. Shamovsky et al. [16,17] suggested the mechanism of eleutheroside B dimerization which was based on the assumption that early in the reaction, two eleutherosides B are arranged by means of an enzyme or another cell matrix so that the planes of their conjugated systems coincide. There may be two cases of hydroxyl group arrangement: on either side of the plane. These different mutual

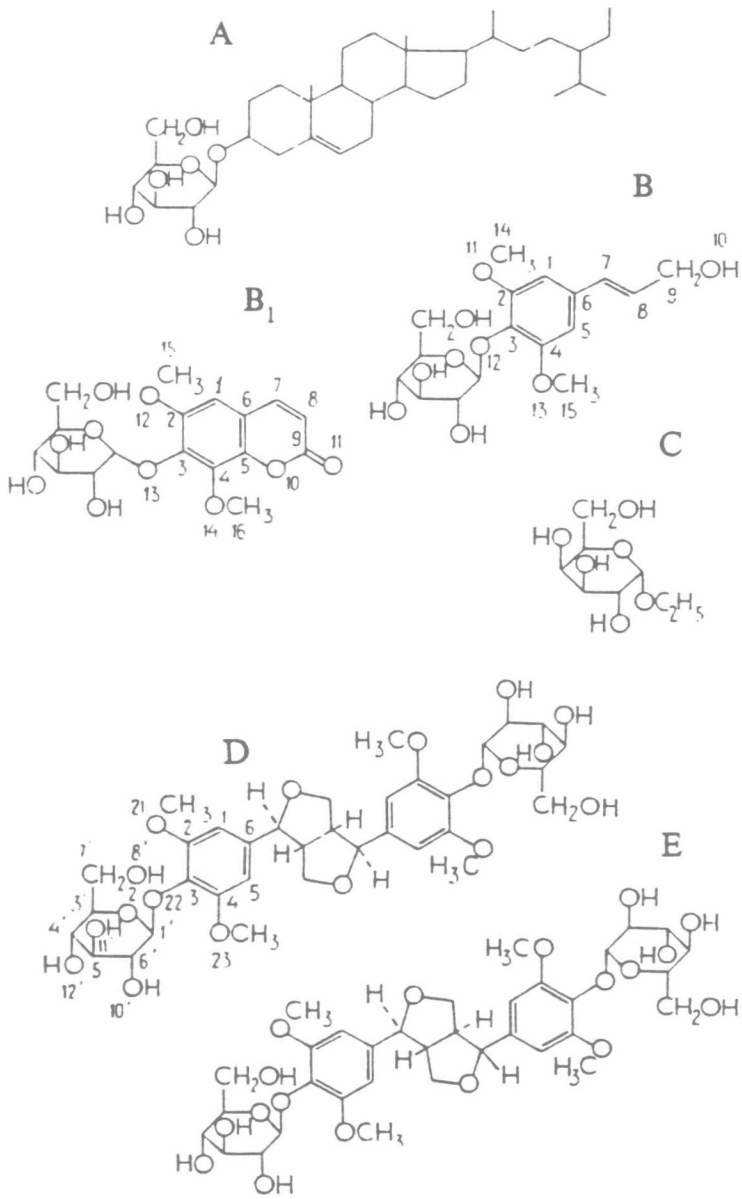


Figure 1. Structural formulas of eleutheroside A—eleutheroside A (daucosterol); B—eleutheroside B (Syringine); B_1—eleutheroside B_1 (7-αD-glycoside of isofraxidine); C—eleutheroside C (ethyl-α-D-galactoside); D—eleutheroside D (di-β-D-glycoside (-) syringaresion); E—eleutheroside E (hypothetical structure).

arrangements of hydroxyl groups are believed to be responsible for various configurations of dimerization products, i.e., eleutherosides D and E that arise from further reactions.

The second group involves eleutheroside A identified with daucosterol and eleutheroside C which is an ethyl-α-D-galactoside. As seen from Figure 1, the glycosides in question are mono- or bi-sides. The monosaccharide residues entering the side chain are terminal. All eleutherosides, except eleutheroside C, contain glucose residues, while eleutherioside C contains galactose. All the glucosides have methoxyl groups. Glycosides or their aglycones are highly labile.

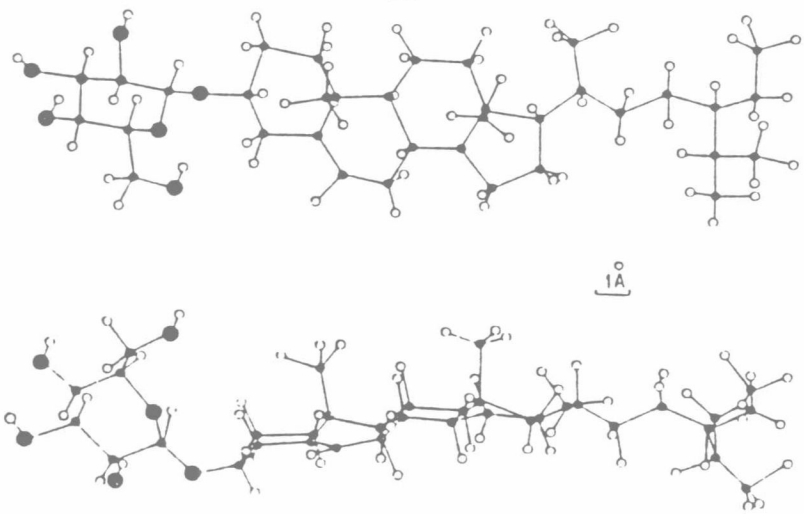
The Eleutherococcus glycosides are not unique, they occur in many other plants that do not belong to the genus Araliaceae. On the other hand eleutherosides bear no resemblance to panaxosides (ginseng glycosides), though they belong to the same genus and have similar activity [7]. The principal work on the chemistry of Eleutherococcus was made in the 1960–1970's in the Russia. Later the results of these investigations were made evident by Wagner et al. [18] who, using thin-layer chromatography and high performance liquid chromatography, showed the presence of eleutherosides B_1, B, E, chlorogenic acid, β-sitosterol, carophylline, isofraxidine, syringaresinole, cesamine, ethyl ether of caffeic acid, and coniferol aldehydein Eleutherococcus extracts. Eleutheroside B was found by the authors in the Eleutherococcus root from Russia and Southern Korea, but it was absent in the plant material obtained from China. The noticeable variability in composition as indicated by N.R. Farnsworth et al. [1] may significantly affect the biological activity of Eleutherococcus extracts, which increases the need for chemical standardization of plant extracts before their biological evaluation.

1.2. Conformation of Eleutherosides

On the basis of the detailed knowledge of eleutheroside configurations (Figure 1), detected by various physical and chemical methods [9–12], I.L. Shamovsky et al. [17] theoretically calculated the conformations of eleutherosides with the method of atom–atom potentials. The choice of this method was due to the great complexity of the tested compounds, but on the other hand, the structural variety of eleutheroside molecules made their additional application and quantum chemical techniques justifiable. Thus, the Huckel method of molecular orbitals was used to calculate the length of chemical bonds and parameters for flexibility of conjugated systems, and the conformations were calculated by minimizing the energy of molecular tension in the atom–atom approximation [19].

Initial results i.e., the set of internal or external (Decartes) coordinates of all atoms of the calculated molecules, were displayed by the authors as the projections of eleutheroside molecules on two orthogonal planes. One of the projections was chosen so that it should retain most of the information about the three-dimensional structure of the molecules, i.e., the projections of atoms should be scattered over the outline plane at a maximum and not prevent from seeing the

A



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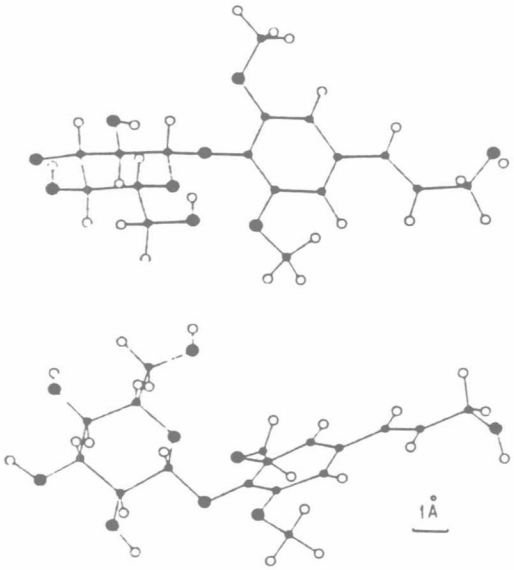

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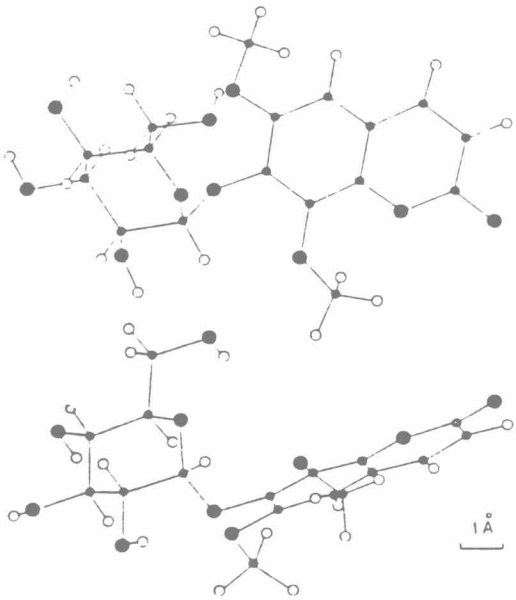

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