NEW SUBSTANCES OF PLANT ORIGIN WHICH INCREASE NONSPECIFIC RESISTANCE[1]

By I. I. Brekhman and I. V. Dardymov

Institute of Biologically Active Substances, Siberian Department of Academy of Sciences of the U.S.S.R., Vladivostok, U.S.S.R.

The problem of increasing nonspecific resistance of an organism to untoward influences of various origin is of great importance. Some effective pharmacological preparations are known to increase the resistance of an organism experiencing severe circulation disorders and deep oxygen hunger, as in the case of extensive surgical operations. Narcotics, phenothiazine derivatives, ganglionic blocking agents, etc., are used for this purpose. However, with administration of these substances the increase of resistance turns out to be incompatible with independent activity of a human organism, whereas an enhanced resistance is not infrequently important for an essentially healthy man, as well as for prophylaxis and medication for various diseases.

The first great success achieved on the pathway to development of medicinal remedies which increase nonspecific resistance was the ascertaining of similar properties in benzimidazol derivatives. N. V. Lazarev and his collaborators found 2-benzyl-benzimidazol (dibazol) to be effective in medication for damage to various regions of the nervous system and to increase nonspecific resistance to adverse influences (1–3). The theoretical basis for separation of a new group of medicinal substances was laid down by Lazarev (4, 5), who phrased the concept of "a state of nonspecifically increased resistance" of the organism (SNIR). The medicinal substances causing SNIR were named "adaptogens".

This comparatively recent history of the discovery of adaptogenic action of dibazol and its analogues had been preceded by attainments of folk medicine of long standing. Corroborative and tonic plants are among the most ancient medicinal remedies of folk medicine in different parts of the world. Even now among some peoples they count for much. We have analysed 158 complex prescriptions of folk medicine of Southeastern Asian countries and found that 116 prescriptions included plants of tonic action (in 31 of them, two plants in each and in 40, from three to seven in each). In all recipes there were incorporated, in various combinations, 189 medicinal plants, tonic action having been ascribed to 46. In the chemical composition of these plants glycosides were prevalent, alkaloids being identified in

[1] The survey of literature pertaining to this review was completed in March 1968.

only 28 per cent of the cases. Medicinal plants of corroborative action were prevalent in recipes for treatment of hypertension, atherosclerosis, diabetes, cancer, tuberculosis, anemia and some other diseases.

Panax ginseng C. A. Mey., which has been known more than 4000 years, occupies a particular place among tonic remedies. Pharmacological investigations have shown that the basic effect in ginseng action is its capacity to increase nonspecific resistance of the organism to various untoward influences (6, 7). Further enrichment of the group of adaptogens has involved utilization of substances of natural origin, rather than chemical synthesis of new compounds. In addition to ginseng, the following plants of the Araliaceae family, viz., *Eleutherococcus senticosus Max., Aralia manshurica Rupr. et Max., Aralia cordata Thunb., Aralia schmidtii Pojark., Echinopanax elatum Nakai, Acantopanax sessiliflorum Rupr. et Max., Kalopanax septemlobum (Thunb.) Koidz* have been studied (8–18). Two plants belong to the Compositae family, viz. *Raponticum carthamoides (Wild.) Iljin* (19, 20) and *Carlina biebersteinnii Bernh.* (21, 22). Special mention is to be made of *Rhodiola rosea L.* of the Crassulaceae and *Shizandra chinensis (Turcz.) Baill.* of the Shizandraceae family (24–26).

The chemical composition of the above plants has been studied in some instances. Six individual glycosides that were given a name of panaxosides were isolated from methanol extracts of the *Panax ginseng* root. (27, 28). Panaxosides were divided into two groups (A, B, C and D, E, F), each of them having the inherent neutral dammaran genin (28). The former group was less polar and contained glycosides poor in sugars, the latter was more polar, with glycosides containing more sugars (29). From the latter group of panaxosides the triterpenoid panaxadiol, was isolated (30); this is a product of native genin transformation (28, 31, 32). From the first group of panaxosides hydrolysis products the triterpenoid, panaxatriol, was isolated (28, 33, 34). On the basis of experimental data a structure for the side chains of panaxosides A, D, E and F was suggested (35, 36).

Six glycosides (eleutherosides) were isolated from the roots of *Eleutherococcus senticosus*. Eleutherosides B, D and E were structurally close, the first being monoglycoside of syringaresinol. Eleutherosides D and E were the two forms of di-β-D-glycoside of syringaresinol, which differed in configuration. Eleutheroside A was identified as daukosterin. Eleutheroside C was ethyl-β-D-galactoside. Later, eleutheroside B_1 was isolated, acid hydrolysis of which released glucose and a genin identified as isofraxidine (7-oxy-6,8,dimethoxy-coumarin) (37–39).

In the roots of *Aralia manshurica* two triterpenoid saponins—glycosides of oleanolic acid called aralosides (40–42) were found.

In the roots of *Aralia schmidtii* were found glycosides, hydrolysis of which also resulted in oleanolic acid. One of the glycosides isolated from this plant was identical with araloside A (43).

Four individual glycosides (acantosides) were isolated from the roots of *Acantopanax sessiliflorum*. Acantosides A and C were respectively mono-

and diglycosides of lignan 2-(4,5-dimethoxy-3-hydroxyphenyl)-6-hydrophenyl-3,7-dioxabicylco-(3.3.0)octane. Acantoside B was mono-β-D-glycopyranoside(−)-syringaresinol; acantoside D being di-β-D-glycopyranoside (−)-syringaresinol. The latter was identified with eleutheroside E from eleutherococcus roots (44–47).

From the roots of *Kalopanax septemlobum,* glycosides called kalopanax-saponins A ($C_{41}H_{66}O_{12} \cdot H_2O$) and B ($C_{59}H_{96}O_{28} \cdot H_2O$) were isolated. Kalopanax-saponin turned out to be bioside of hederagenin. Kalopanax-saponin was a pentaoside, that alkaline hemolysis transformed into kalopanax-saponin A (48).

The chemical composition of *Raponticum carthamoides* has not been studied yet. In different parts of *Carlina biebersteinii,* from 0.6 to 3.4 per cent of flavone glycosides were found (49).

From the roots of *Rhodiola rosea* a rectified preparation "rhodosin" was isolated, in which four substances of lactonic character were found (50).

From the seed of *Shizandra chinensis,* shizandrin (*2',3',4',1'',2'',3''*-hexamethoxy-6,7-dimethyl-1:2,3:4-dibenzo-cyclooctadien-1,3-ola-6) and gamma-shizandrin with the same carbon skeleton were isolated (51–53). As is seen from the above have been considered to the data, glycosides were prevalent in plants that increase the nonspecific resistance of the organism.

Only those preparations that meet the following requirements may be included in the group of adaptogens (11): (*a*) An adaptogen should be innocuous and cause minimal disorders in the physiological functions of an organism; (*b*) The action of an adaptogen should be nonspecific, i.e., it should increase resistance to adverse influences of a wide range of factors of physical, chemical and biological nature; (*c*) An adaptogen may possess normalizing action irrespective of the direction of the foregoing pathologic changes.

In conformity to the above-mentioned requirements *Eleutherococcus senticosus* is placed first, followed by *Panax ginseng, Raponticum carthamoides* and *Rhodiola rosea.* The adaptogenic action of the principal active substances—glycosides—has been studied thoroughly in regard to the first two plants. The rest of the plants and their active substances have been studied considerably less.

The toxicity of these plants which increase the nonspecific resistance of organisms is very low. For the roots of *Panax ginseng, Eleutherococcus senticosus, Echinopanax elatum, Acantopanax sessiliflorum, Raponticum carthamoides* and *Rhodiola rosea,* the LD_{50} is 10 to30 g/kg (6, 8, 13, 18). The toxicity of *Aralia manshurica* and *A. schmidtii* is 10 to 15 times greater (13, 54). According to our findings the LD_{50} for the sum of panaxosides was 1.4 g/kg, for the sum of eleutherosides 4.75 g/kg, and for the sum of aralosides (55) from *Aralia manshurica* 0.47 g/kg. The toxicity of shizandrin is also low, for mice did not die from a dose of 1 g/kg (56).

The excitant action (augmentation of spontaneous motor activity) was

identified with *Aralia manshurica* and *Echinopanax elatum;* almost all the plants possessed antinarcotic action. *Eleutherococcus senticosus, Panax ginseng, Raponticum carthamoides* and *Aralia manshurica* showed a slight activating action on the EEG of intact rabbits and diminished the depressant action of chloral hydrate, medinal and aminasin. *Panax ginseng* and *Eleutherococcus senticosus* chiefly intensified the inner inhibitory processes in the cortex. In the case of administration of glycosides during an acute experiment on an animal a transitory and slight hypotensive effect was observed. An effect on the vessels was observed only with large doses. Essentially noteworthy was the fact that with doses which increased the nonspecific resistance of an organism the plants and substances extruded from them did not cause significant disorders in the normal functions of an organism (6–8, 13, 16–18, 20, 54, 55, 57–61).

Panax ginseng, Eleutherococcus senticosus, Raponticum carthamoides and *Rhodiola rosea* contributed to a more sparing use of carbohydrates and to an enhanced resynthesis of glycogen and high energy phosphorus compounds. This action was found to reveal itself unequivocally under physical strain (11, 20, 62–64). Numerous data on the increase of body weight (6, 9, 11, 65), on restoration of blood albumin after massive bleeding (9), on stimulation of immune body production (67–70), testified to a peculiar anabolic action. Its characteristic trait was the fact that it manifested itself only in the presence of an appropriate background and, contrary to steroid anabolic agents, was not accompanied by virilization.

The overwhelming majority of adaptogenic effects became apparent only on a specific background, and when the resistance of the organism was diminished or the organism was taxed with extra demands. One of the most important indices of the action of adaptogens was their capacity to increase efficiency both after a single (stimulant action) or prolonged (tonic action) administration. This was natural, for efficiency is an integral and very sensitive index of the general state of the organism. Data were obtained on the increase of physical and mental efficiency of man after single or prolonged administration of the preparations from *Panax ginseng* (6, 7, 13), *Eleutherococcus senticosus* (8, 9, 11, 13), *Echinopanax elatum* (13), *Aralia manshurica* (13), *Acantopanax sessiliflorum* (71), *Raponticum carthamoides* (57, 58), *Carlina biebersteinii* (72, 73), *Rhodiola rosea* (23, 62, 74, 75) and *Shizandra chinensis* (56, 76). Stimulant action of preparations from the above-mentioned plants differed in principle from that of benzedrine-like compounds. Substances of natural origin differed from the latter in low toxicity, and absence of a pronounced excitant action. They did not lead to disturbances in the normal sleep of man, or in falling asleep.

Active substances isolated from some plants (glycosides) were of a more pronounced stimulant action than infusions or extracts. This was proved by experiments with white mice swimming in water (6, 11, 13, 26, 56–58) and more clearly in a special device, in which mice were made to run up an endless rope (77). In this method each preparation was tested at three dos-

age levels, which offered the possibility of finding the amount of the substance that increased by 33 per cent the work duration up to the onset of complete fatigue. This amount of the substance was accepted as one "stimulant unit of action" (SUA_{33}). In comparison with liquid extracts (50 to 70 SUA_{33}), the panaxosides from the *Panax ginseng* roots (700 to 6600 SUA_{33}) and their genins (2000 to 5000 SUA_{33}), and also various eleutherosides (2000 to 8000 SUA_{33}) isolated from the *Eleutherococcus* roots, were of an incomparably stronger stimulant action (11, 78). This was attributable to shizandrin (80), flavone glycosides from *Carlina biebersteinii* (81), and rhodosin from *Rhodiola rosea* (75).

A second feature of the action of adaptogens concerned the lack of specificity of their action as defined by their capacity to increase the organism's resistance to various adverse factors of a physical nature (cooling, overheating, immobilisation, enhanced motor activity, overload on a centrifuge, increased or decreased barometric pressure, and ultraviolet or ionizing radiation), of a chemical (various toxic, narcotic, hormonal, and anticancerous), and of a biological nature (foreign sera, bacteria, transplanted tumours, etc.) Many facts concerning this kind of universal defence action were obtained for *Eleutherococcus senticosus, Panax ginseng, Raponticum carthamoides, Rhodiola rosea* and *Carlina biebersteinii* (6–12, 14, 19, 20, 23, 65, 74).

Data characterizing the universality of the action of some adaptogens were obtained in experimental therapeutic researches into some pathologic processes.

Eleutherococcus senticosum and *Panax ginseng* were found to possess radioprotective and medicinal action in a single X-ray irradiation of animals (11, 82). In a prolonged irradiation (total doses of 1620 to 7000 r) *Panax ginseng* and *Eleutherococcus senticosus* doubled the lifetime of rats, improved the state of blood and other indices. *Eleutherococcus senticosus* in combination with antibiotics lengthened the lifetime of irradiated rats (60 days; total dose 3,000 r) threefold (10, 11).

In treatment of alloxan-induced diabetes, *Eleutherococcus* was found to impede a loss in body weight of rats, to reduce the concentration of sugar in urine two- or threefold and to the same extent prolong the lifetime of animals (83, 84). Experiments with *Panax ginseng* (83) and *Aralia manshurica* (85) in medication for alloxan-induced diabetes were also positive.

Eleuthercoccus senticosus was tested in experimental oncological researches (86, 87). Its preparations were found to inhibit the urethane-induced lung adenomas in mice (88), tumors of the thyroid gland in rats induced by 6-methylthiouracil (86), and myeloid leukemia in mice induced by indole (89). Evidence was obtained of a decrease of transplantability of Ehrlich tumours (90–92), lymphosarcoma LIO-1 in mice (93), and some other transplanted tumours. A substantial inhibition of the metastasizing process manifested itself in some cases (86, 87, 94). Data were obtained on decrease of the formative process of spontaneous tumours of the mammary

gland (95) and spontaneous leukemia in mice (96, 97). These findings and also radioprotective and antitoxic action towards anticancer preparations made the use of *Eleutherococcus* extract promising in a complex therapy of cancer carriers. In parallel with *Eleutherococcus senticosus* the preparations of *Panax ginseng* (86, 90, 91) have been studied, but the action of the latter was found to be weaker and inconstant. Other plants have not been investigated in this regard.

A third and more important characteristic of an adaptogen was its normalization action which revealed itself irrespective of the direction of the previous pathologic shifts. *Eleutherococcus senticosus* was experimentally proved to impede hypertrophy (ACTH) and atrophy (cortison) of the adrenals, hypertrophy (thyreoidin) and atrophy (6-methylthiouracil) of the thyroid gland, to reduce the sugar level in alimentary (glucose) and adrenal hyperglycaemia and to increase it in hypoglycaemia induced by insulin. The normalization action was obtained in leucocytosis (parenteral administration of milk) and leucopenia (endotoxin of dysenteric microbes), in erythrocytosis (cobaltous nitrate) and erythropenia induced by phenylhydrazine (11, 12, 98). Similar data were obtained for *Panax ginseng, Rapontiicum carthamoides,* and *Rhodiola rosea* (19, 20, 23, 74, 98).

Accumulation of facts on the universality of the action of *Eleutherococcus senticosus* and some other plants urgently demanded elucidation of the mechanism of adaptogenic effect. Firstly, the action of adaptogens in stress, a general araptogenic reaction normally appearing under the most diverse influences on the organism (99), has been studied. Immobilization and increased muscle loads (swimming of rats) of different duration; intoxication (epinephrine, sodium salicylate, ACTH), unilateral adrenalectomy, etc., were used as stressors (11, 12, 92, 100, 101). It was established that *Eleutherococcus* preparations altered anatomic and biochemical manifestations, characteristic of the alarm stage of stress: a reduction of activation of the adrenal cortex, also thymicolymphatic involution and a number of bleeding ulcerations in the stomach. Antialarm action was natural to *Panax ginseng* also (100, 102–104). Direct data on a similar action for other plants that increase nonspecific resistance have not been obtained.

The antialarm action was established for the representatives of both groups of glycosides of ginseng roots—panaxosides C and F (79), and genin derivatives, of closely related structure. It manifested itself in reduction of hypotrophy of the adrenals and their loss of cholesterol and ascorbic acid. Excretion of 17-ketosteroids in urine, highly increased in stress, now diminished. A smaller involution of the organs of the thymicolymphatic system and abatement of many catabolic shifts in the organism were observed. Glycosides of *Eleutherococcus* root of varying structure revealed the antialarm action. It was mostly expressed in eleutheroside E, weakly in eleutheroside B_1 and was completely absent in eleutheroside C (79). Thus, the antialarm action was associated with certain chemical structures.

It might have been assumed that the antialarm action of adaptogens, along with all other manifestations of stress, would lessen its positive influence on resistance of the organism. However, in stress, adaptogens may increase nonspecific resistance rather than lessen it. For example, in one experiment (11, 12) two groups of rats were made to swim in water. A dose of 0.2 ml/g of *Eleutherococcus* extract was injected intraperitoneally into each of half the rats of each group. After five hours half of the rats of each group were killed. In comparison with the adrenals of rats that were not made to swim (16.5 ± 0.75 mg/100 g) a five-hour swimming caused a marked hypertrophy of the adrenals in the controls (19.6 ± 1.14 mg/100 g) which was almost completely prevented by *Eleutherococcus* extract (16.8 ± 0.62 mg/100 g). The content of ascorbic acid in the adrenals in control animals was 396 mg per cent, and after swimming was reduced to 257 ± 31 mg per cent. After administration of extract, it was 338 ± 13.5 mg per cent. All this testified to a clear antialarm action of *Eleutherococcus* extract. At the same time *Eleutherococcus* increased the resistance of the rats, for, in comparison with controls, they were able to swim 52 min. longer (9.2 per cent) until complete fatigue (death).

The analysis of all the data leads us to the conclusion that SNIR appearing under the influence of adaptogens was not realized through a general adaptation reaction and was not identical with an enhancement of nonspecific resistance in the alarm stage of stress. SNIR in contrast to the alarm stage of stress was always beneficial to the organism, might last comparatively long, and was not accompanied by pathologic changes. The function of the adrenal cortex at SNIR did not alter (11, 12, 100).

The protective effect of *Eleutherococcus* and some other adaptogens in stress made their universality comprehensible to a certain extent but did not elucidate the mechanism of their action. The study of intimate mechanisms of adaptogenic action of a number of substances is the subject of further investigations. In addition, it is necessary to take into account the following circumstances: (*a*) A number of effects of adaptogens of plant origin are observed on the cell. Extracts from the roots of *Panax ginseng* and *Eleutherococcus senticosus* stimulate the growth and multiplication of some protozoa, bacteria (105, 106) and yeast cells (106, 107). Extracts from *Eleutherococcus senticosus, Echinopanax elatum* and *Aralia manshurica* exert protective action in the case of irradiation of diploid yeast *Saccharomyces vini* (108). *Eleutherococcus* and ginseng extracts and all the panaxosides isolated from the latter revealed a marked protective effect when erythrocytes were affected by artificial radiomimetic substances (oxidized oleic acid) (109). (*b*) Active substances of *Eleutherococcus senticosus, Panax ginseng* and *Aralia manshurica* were shown to possess antiradical and antioxidant action (108, 110). It must be noted that the prophylactic and medicinal effects were obtained in pathologic states (stress, irradiation, cancer) in which disturbances through the action of free radicals played a significant

role (111–113). (*c*) The above-mentioned anabolic action of a number of adaptogens, particularly their stimulation of the production of immune bodies and other effects make one assume that the processes of biosynthesis of protein and nucleic acid played a significant part in the mechanism of their action from the standpoint of the concept of plastic provision of functions (114). It was these processes that turned out to be most significant in the mechanism of adaptogenic action of dibazol (115).

Thus, the influence on the processes occurring at the cellular level, the antioxidant action of a number of adaptogens, and their influence on the processes of biosynthesis of protein and nucleic acids, offer the possibility of attaining a fuller comprehension of the mechanisms of adaptogenic action. The fact that the mechanism of action has not been thoroughly studied is not an obstacle to separation of a new group of pharmacological substances that increase the nonspecific resistance of an organism.

LITERATURE CITED

1. Lazarev, N. V., *VII Vsesojuzniy s'ezd fiziologov, biokhimikov i farmakologov* (7th All-union congr. of physiol., biochem., pharmacol.), 579, Medgiz, Moscow, (1947)
2. Rozin, M. A., *Lekarstvennie sredstva dlja vosstanovitelnoy terapii i profilaktiki zabolevaniy nervnoi sistemy* (Medicinal remedies for restoration therapy and prophylaxis of diseases of the nervous system), Izdanie Voenno-morskoy Medicinskoy Acad., Leningrad, 51 pp. (1951)
3. Anosov, N. N., Rozin, M. A., *Prozerin, ezerin, dibazol i ikh primenenie v nevropatologii* (Prozerin, ezerin, dibazol and their use in neuropathology) Medgiz, Leningrad, 196 pp. (1956)
4. Lazarev, N. V., *Farmacol. Toxicol.*, **21**, 3, 81–86 (1958)
5. Lazarev, N. V., Ljublina, E. I., Rozin, M. A., *Patol. Fiziol. Eksperim. Terapia*, **3**, 4, 16–21 (1959)
6. Brekhman, I. I., *Zhen-shen (Panax ginseng)*, Medgiz, Leningrad, 182 pp. (1957)
7. Brekhman, I. I., *Med. Sci. Serv.*, **4**, 17–26, July (1967)
8. Brekhman, I. I., *Izv. Sibirsk. Otdelenia Akad. Nauk SSSR*, **9**, 113–22 (1960)
9. Brekhman, I. I., *Proc. 2nd Intern. Pharmacol. Meet.*, 97–102, Prague, 20–23 Aug. 1963, Pergamon Press, Oxford, Czechoslovak Medical Press, Prague (1965)
10. Brekhman, I. I., Majanskiy, G. M., *Izv. Akad. Nauk SSSR, Ser. Biol.*, **5**, 762–65 (1965)
11. Brekhman, I. I., *Eleuterokokk (Eleutherococcus)*, Izdatelstvo "Nauka", Leningrad, 186 pp. (1968)
12. Brekhman, I. I., Kirillov, O. I., *Rast. Resursy*, **4**, 1, 3–13 (1968)
13. Brekhman, I. I., *Materialy k izucheniju zhen-shenja i drugih lekarstvennih pasteniy Dalnego Vostoka*, (Materials for the study of *Panax ginseng* and other medicinal plants of the Far East), **5**, 219–27, Primorskoe knizhnoe izdatelstvo, Vladivostok, (1963)
14. Fruentov, N. K., *Materialy k izucheniju zhen-shenja i limonnika* (Materials for the study of *Panax ginseng* and *Shizandra chinensis*), **3**, 133–40, Izdanie Akad. Nauk SSSR, Leningrad, (1958)
15. Turova, A. D., Chukicheva, M. N., Nikolskaja, B. S., *Lekarstvennie sredstva rastitelnogo proishozhdenija* (Medicinal remedies of plant origin), Medgiz, Moscow, 176 pp. (1954)
16. Turova, A. D., Aleshkina, Ja. A., *Lekarstvennie sredstva iz rasteniy* (Medicinal remedies from plants) Medgiz, Moscow, 314 pp. (1962)
17. Turova, A. D., *Lekarstvennie rastenija SSSR i ih preminenie* (Medicinal plants of the USSR and their use), Izdatelstvo "Medicina", Moscow, 692 pp. (1967)
18. Zvereva, A. V., *Eleuterokokk i drugie*

adaptogeni iz dalnevostochnih rasteniy (*Eleutherococcus* and other adaptogens of Far Eastern plants), Dalnevostochnoe knizhnoe izdatelstvo, Vladivostok, 257–60, (1966)

19. Saratikov, A. S., Pichurina, R. A., *Izv. Sibirsk. otdelenija Akad. Nauk SSSR, Ser. Biol. Med. Nauk,* **4,** 113–19 (1965)
20. Saratikov, A. S., *Stimulatori centralnoy nervony sistemi* (Stimulators of central nervous system), 3–23, Izdatelstvo Tomskogo Univ., Tomsk (1966)
21. Belenkiy, E. E., Kolla, V. E., *Materialy k izucheniju zhen-shenja i drugih lekarstvennih rasteniy Dalnego Vostoka* (Materials for the study of *Panax ginseng* and other medicinal plants of the Far East), **5,** 119–22, Primorskoe knizhnoe izdatelstvo, Vladivostok (1963)
22. Kolla, V. E., *Izv. Estestv. Inst. Permsk. Univ.,* **14,** 6, 209–13 **(1963)**
23. Zotova, M. I., Krilov, G. V., Saratikov, A. S., *Izv. Sibirsk. Otdelenija Akad. Nauk SSSR, ser. Biol. Med. Nauk,* **8,** 111–19 (1965)
24. Lebedev, A. A., *Materialy k izucheniju zhen-shenja i limonnika* (Materials for the study of *Panax ginseng* and *Shizandra chinensis*), **2,** 178–88, *Izd. Akad. Nauk SSSR,* Moscow-Leningrad (1955)
25. Volicer, L., Janku, I., Motl, O. Jiricka, Z., *Proc. 2nd Intern. Pharmacol. Meet.,* 29–38, Prague, 20–23 August 1963, Pergamon Press, Oxford, Czechoslovak Medical Press, Praha (1965)
26. Lupandin, A. B., *O vlijanii limonnika na chustvitelnost organizma k nekotorym neblagoprijatnim vozdeistvijam* (On influence of *Shizandra chinensis* on sensitivity of the organism to some untoward effects), dissertacija, Khabarovsky gosudarstvenniy medicinskiy institut, Khabarovsk, 230 pp. (1967)
27. Elyakov, G. B., Strigina, L. I., *Izv. Sibirsk. otdelenija Akad. Nauk SSSR,* **6,** 126 (1962)
28. Elyakov, G. B., Strigina, L. I., Uvarova, N. I., Vaskovsky, V. E., Dzizenko, A. K., Kochetkov, N. K., *Tetrahedron Letters,* **48,** 3591 **(1964)**
29. Uvarova, N. I., Gorshkova, R. P., Elyakov, G. B., *Izv. Akad. Nauk SSSR, Ser. Khim. Nauk,* **10,** 1850–52 (1963)
30. Shibata, S., Fujita, M., Itokawa, H., Tanaka, O., Ishii, T., *Tetrahedron Letters,* **10,** 419–22 (1962)
31. Shibata, S., Tanaka, O., Sado, M., Tsushima, S., *ibid.,* **12,** 725–80 (1963)
32. Shibata, S., Fujita, M., Itokawa, H., Tanaka, O., Ishii, T., *Chem. Pharm. Bull.* (Tokyo), **11,** 6, 759–61 (1963)
33. Shibata, S., Tanaka, O., Sôma, K., Iida, Y. (Miss), Ando, F., Nakamura, H., *Tetrahedron Letters,* **3,** 207–13 (1965)
34. Elyakov, G. B., Strigina, L. I., Kochetkov, N. K., *Dokl. Akad. Nauk SSSR,* **158,** 4, 892–95 **(1964)**
35. Elyakov, G. B., Strigina, L. I., Kochetkov, N. K., *Khim. Prirodnih Soedin.,* **3,** 149–52 (1965)
36. Elyakov, G. B., Uvarova, N. I., Gorshkova, R. P., Ovodov, Yu. S., Kochetkov, N. K., *Dokl. Akad. Nauk SSSR,* **165,** 6, 1309–12 **(1965)**
37. Ovodov, Yu. S., Ovodova, R. G., Solov'eva, T. F., Elyakov, G. B., Kochetkov, N. K., *Khim. Prirodnih Soedin.,* **1,** 3–7 (1965)
38. Ovodov, Yu. S., Frolova, G. M., Elyakova, L. A., Elyakov, G. B., *Izv. Akad. Nauk SSSR, Ser. Khim.,* **11,** 2065–67 (1965)
39. Ovodov, Yu. S., Frolova, G. M., Nefedova, M. Yu., Elyakov, G. B., *Khim. Prirodnih Soedin.,* **1,** 63–64 **(1967)**
40. Kochetkov, N. K., Khorlin, A. J., Vaskovsky, V. E., Zhvirblis, V. E., *Zh. Obshch. Khim.,* **31,** 658 (1961)
41. Kochetkov, N. K., Khorlin, A. J., Vaskovsky, V. E., *Tetrahedron Letters,* **16,** 713 (1962)
42. Khorlin, A. J., *Dokl. Akad. Nauk SSSR,* **150,** 1229 (1963)
43. Elyakov, G. B., Khorlin, A. J., Strigina, L. I., Kochetkov, N. K., *Izv. Akad. Nauk SSSR, Otdelenie Khim. Nauk,* **9,** 1605–08 (1962)
44. Elyakova, L. A., Elyakov, G. B., *Izv. Akad. Nauk SSSR, Ser. Khim.,* **3,** 555–56 (1965)
45. Elyakova, L. A., Dzizenko, A. K., Elyakov, G. B., *Dokl. Akad. Nauk SSSR,* **165,** 562–65 (1965)
46. Elyakova, L. A., *Khimicheskoe issledovanie lignanov i lignanovih*

glikozidov akantopanaxa (Chemical investigation of lignan and lignan glycosides of acantopanax), Dissertacija, Dalnevostochniy Gosudarstvenniy Univ., Vladivostok, 130 pp. (1966)

47. Elyakova, L. A., Dzizenko, A. K., Sova, V. V., Elyakov, G. B., *Khim. Prirodnih Soedin.*, **1**, 32–34 (1966)
48. Khorlin, A. J., Venijaminova, A. G., *Izv. Akad. Nauk SSSR, Otdelenie Khim. Nauk*, **8**, 1447 (1964)
49. Sijuzeva, Z. F., *Izv. Estestv. Inst. Permsk. Univ.*, **14**, 8, 45–48 (1966)
50. Krasnov, E. A., Duvidzon, L. M., Khnikina, L. A., Evstigneeva, R. P., (See ref. 20), 72–76 (1966)
51. Balandin, D. A., *Materialy k izucheniju stimulirujushchih i tonizirujushchih sredstv—kornja zhenshenja i limonnika* (Materials for the study of stimulating and tonic remedies—of *Panax ginseng* root and *Shizandra chinensis*), 45–50, Izdanie Dalnevostochnogo filiala Akad. Nauk SSSR, Vladivostok (1951)
52. Kochetkov, N. K., Khorlin, A. J., Chizhov, O. S., *Zh. Obshch. Khim.*, **31**, 3454–60 (1960)
53. Kochetkov, N. K., Khorlin, A. J., Chizhov, O. S., Sheichenko, V. I., *Izv. Akad. Nauk SSSR, Otdelenie Khim. Nauk*, **5**, 850–56 (1962)
54. Seifulla, H. I., *Lekarstvennie sredstva iz rasteniy* (Medicinal remedies from plants), Medgiz, Moscow, 278–86 (1962)
55. Sokolov, C. J., *Lekarstvennie sredstva iz rasteniy* (See ref 54) 270–78 (1962)
56. Lebedev, A. A., *Skhizandrin—novoe stimulirujushchee sredstvo iz plodov kitaiskogo limonnika* (Skhizandrin—a new stimulating remedy from the fruits of *Shizandra chinensis*), Dissertacija, Tashkentskiy medicinskiy institut, Tashkent (1967)
57. Cherikovskaja, T. J., Mikheeva, A. F., *Aptech. Delo*, **1**, 61–62 (1952)
58. Melnikova, T. A., Rozova, E. S., *Aptech. Delo*, **7**, 33–34 (1958)
59. Marina, T. F., (See ref. 20) 24–30 (1966)
60. Zyrjanova, T. M., (See ref. 20) 37–43 (1966)
61. Saratikov, A. S., Marina, T. F., Kaliko, I. M., *Isv. Sibirsk. Otdelenija Akad. Nauk SSSR, Ser. Biol. Med. Nauk*, **8**, 120–25 (1965)
62. Salnik, B. Yu., Telesheva, V. A., *Materialy pervoi nauchnoi konferencii centralnoy nauchno-issledovatelskoy laboratorii Tomskogo medicinskogo instituta* (Materials of the first scientific conference of the scientific-research laboratory of Medical Institute of Tomsk), 184–85, Izdatelstvo Tomskogo Univ. Tomsk (1964)
63. Salnik, B. Yu., (See ref. 20) 44–50 (1966)
64. Feoktistova, G. I., (See ref. 20) 55–58, (1966)
65. Brekhman, I. I., Bikhovcova, T. L., Ratimov, B. N., Suprunov, N. I., Fedorov, B. T., *Izv. Sibirsk Otdelenija Acad. Nauk SSSR*, **11**, 123–28 (1962)
66. Polozhenceva, M. I., Bikhovcova, T. L., *Itogi izuchenija eleuthero kokka v Sovetskom Sojuze* (Summary of study *Eleutherococcus* in the Soviet Union), 48–49, Izdanie Dalnevostochnogo filiala Akad. Nauk SSSR, Vladivostok (1966)
67. Sagaidan, L. P., Pazninova, O. G., (See ref. 20) 97–98 (1966)
68. Tripolitova, A. A., Beketova, Z. P., Voronina, L. D., Zinger, G. V., Sverdlova, L. M., (See ref. 20) 85–90 (1966)
69. Fedorov, Yu. V., Vasilieva, O. A., Vasiliev, N. V., (See ref. 20) 99–105 (1966)
70. Cherkashin, G. V., (See ref. 20) 91–96 (1966)
71. Zvereva, A. V., *Eleuterokokk i drugie adaptogeni iz dalnevostochnih rasteniy* (*Eleutherococcus* and other adaptogens from Far-Eastern plants), 261–65, Daenevostochnoe knizhnoe izdatelstvo, Vladivostok (1966)
72. Kolla, V. E., Zalesov, V. S., Belenkiy, E. E., *Izv. Estestv. Inst. Permsk. Univ.*, **14**, 6, 203–207 (1963)
73. Kolla, V. E., Zhiganov, L. P., *Izv. Estestv. Inst. Permsk. Univ.*, 49–51 (1966)
74. Zotova, M. I., (See ref. 20) 67–70 (1966)
75. Aksenova, R. A., Zotova, M. I., Nekhoda, M. F., Cherdincev, S. G., (See ref. 20) 77–79 (1966)
76. Lebedev, A. A., *Materialy k izucheniju stimulirujushchih i tonizirujushchih sredstv—kornja zhen-*

shenja i limonnika (Materials for the study of stimulating and tonic remedies of *Panax ginseng* root and *Shizandra chinensis*), 103–108, Izdanie Dalnevostochnogo filiala Akad. Nauk SSSR, Vladivostok (1951)

77. Brekhman, I. I., Grinevich, M. A., Glazunov, G. I., *Soobshch. Dalnevost. Filiala Akad.* Nauk SSSR, **19**, 135–38, Vladivostok (1963)
78. Brekhman, I. I., Dardymov, I. V., Dobrjakov, Yu. I., *Farmakol. Toksikol.*, **29**, 2, 167–71 (1966)
79. Brekhman, I. I., Dardymov, I. V., *Proc. Pacific Sci. Congr., 11th*, **8**, 11, (1966)
80. Lebedev, A. A., *Materialy k izucheniju stimulirujushchih sredstv—kornja zhen-shenja i limonnika* (Materials for the study of stimulating and tonic remedies of *Panax ginseng* and *Shizandra chinensis*), **1**, 109–117, Izdanie Dalnevostochnogo filiala Akad. Nauk SSSR, Vladivostok (1951)
81. Kolla, V. E., Sjuzeva, Z. F., Zhiganova, L. P., *Materialy tretey konferencii centralnoy nauchno-issledovatelskoy laboratorii Tomskogo medicinskogo instituta* (Materials of the third conference of the central scientific research laboratory of the Medical institute of Tomsk), 92–94, Izdatelstvo Tomskogo Univ., Tomsk (1966)
82. Brekhman, I. I., Oskotsky, L. I., Khakham, A. I., *Med. Radiol.*, **2**, 33–36 (1960)
83. Bezdetko, G. N., Smolina, T. M., Shuljateva, L. D., *Materialy vtorogo soveshchanija po issledovaniju lekarstvennih rasteniy Sibiri i Dalnego Vostoka* (Materials of the second meeting on study of medicinal plants of Siberia and Far East), 11–12, Izdatlstvo Tomskogo universiteta, Tomsk (1961)
84. Bezdetko, G. N., *Eleuterokokk i drugie adaptogeny iz dalnevostochnih rasteniy* (*Eleutherococcus* and other adaptogens from Far-Eastern plants), 81–84, Primorskoe knizhnoe izdatelstvo, Vladivostok (1966)
85. Aleshkina, J. A., *Lekarstvennie sredstva iz rasteniy* (See ref. 54) 258–63 (1962)
86. Lazarev, N. V., *Vopr. Onkol.*, **11**, 12, 48–54 (1965)
87. Lazarev, N. V., Brekhman, I. I., *Med. Sci. Serv. (India)*, **4**, 9–13, September (1967)
88. Dzioev, F. K., *Vopr. Onkol.*, **11**, 9, 51–54 (1965)
89. Stukov, A. N., *Vopr. Onkol.*, **13**, 1, 94–95 (1967)
90. Mironova, A. I., *Vopr. Onkol.*, **9**, 1, 42–44 (1963)
91. Jaremenko, K. V., *Vopr. Onkol.*, **9**, 8, 60–65 (1963)
92. Jaremenko, K. V., Moskaljuk, K. G., *Vopr. Onkol.*, **13**, 9, 65–69 (1967)
93. Stukov, A. N., *Vopr. Onkol.*, **12**, 7, 57–60 (1966)
94. Tsirlina, E. V., *Vopr. Onkol.*, **11**, 10, 70–77 (1965)
95. Maljugina, L. L., *Vopr. Onkol.*, **12**, 7, 53–57 (1966)
96. Stukov, A. N., *Vopr. Onkol.*, **11**, 12, 64–65 (1965)
97. Stukov, A. N., *Vopr. Onkol.*, **12**, 11, 124 (1966)
98. Pichurina, R. A., *Deistvie ekstraktov zhen-shenja, eleuterokokka i levzei pri nekotorih patologicheskih reakcijah perifericheskoi krovi* (Effect of *Panax ginseng*, *Eleutherococcus* and Leuzea extracts in some pathological reactions of peripheral blood), Dissertacija, Tomskiy medicinskiy institut, Tomsk (1963)
99. Selye, H., *Nature*, **3479**, 32–40 (1936)
100. Kirillov, O. I., *Opyt farmakologicheskoy reguljacii stressa* (Experience of pharmacological regulation of stress) Dalnevostochnoe knizhnoe izdatelstvo, Vladivostok, 106 pp. (1966)
101. Jaremenko, K. V., *Problemy sovremennoy onkologii* (Problems of modern oncology), 59–63, Izdanie Nauchno-issledovatelskogo instituta onkologii, Leningrad (1967)
102. Petkov, V., Staneva-Stoicheva, D., *Proc. 2nd Intern. Pharmacol. Meet.*, 39–45, Prague, 20–23 August 1963, Pergamon Press, Oxford; Czechoslovak Medical Press, Praha, 1965.
103. Zhou, J. H., Fu, F. Y., Lei, H. P., *ibid.*, 17–25 (1965).
104. Sung, Chen-Yi, Chi, Hsin-chüan, *Acta Physiol. Cinica*, **22**, 155–158 (1958)
105. Gavriljuk, B. K., *Materialy k izucheniju zhen-shenja i limonnika*

(Materials for the study of *Panax ginseng* and *Shizandra chinensis*), **4,** 209–12, Izdanie Dalnevostochnogo filiala Akad. Nauk SSSR, Vladivostok (1960).

106. Gavrilov, K. I., *Materialy k izucheniju zhen-shenja i drugih lekarstvennih rasteniy Dalnego Vostoka* (Materials for the study of *Panax ginseng* and other medicinal plants of the Far East) **5, 153–55**, Primorskoe knizhnoe izdatelstvo, Vladivostok (1963)
107. Krasilnikova, A. P., *Simposiumy po eleuterokokku i zhen-shenju* (Symposium on *Eleutherococcus* and *Panax ginseng*), 18, Izdanie Dalnevostochnogo filiala Akad. Nauk SSSR, Vladivostok (1964)
108. Tkhor, L. F., Taranenko, G. A., Kozlov, Yu. P., *Tr. Mosk. Obshch. Ispitateley Prirody,* **16,** *73–77* (1966)
109. Brekhman, I. I., Ganenko, V. A., *Radiobiologija,* **8,** (in press) (1968)
110. Ivanov, I. I., Kozlov, Yu. P., Tkhor, L. F., *Bull. Mosk. Obshchestva Ispitateley Prirody,* **70,** 1, 167–68 (1965)
111. Azhipa, J. A., *Biofizika,* **10,** 3, 500–06 (1965)
112. Kolomiyceva, I. K., Kajushin, L. P., Kuzin, A. M., *Dokl. Akad. Nauk SSSR,* **147,** 4, 251–53 (1962)
113. Sirkin, A. B., *Usp. Sovrem. Biol.,* **49,** 3, 303–19 (1960)
114. Meerson, F. Z., *Plastichoskoe obespechenie funkciy organisma* (Plastic provision of functions in organism), Izdatelstvo "Nauka", Moscow, 317 pp. (1967)
115. Rozin, M. A., *Kletka i nespecificheskaja soprotivljaemost organizma* (Cell and nonspecific resistance of the organism), Izdatelstvo "Nauka", Leningrad, 147 pp. (1967)