Selected Strains of Ginseng with Ge-organic Compounds and its Effects.

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ABSTRACT

The first original inducer of interferon had been synthesized in Russia in 1965-1967. It was 2-carboxiethyl-germanysesquioxan (Lx-13) and other-1 hydroxigermanytrans-monohydral (Lx-5), These compounds have very high induction of interferon.The strain of *Panax ginseng* C. A. Meyer was recultivated on medium with different concentiation of (Lx-13) and (Lx-5) many times. The strain was stabilized when biomass of cells contain of the Ge form $10x10^{-3}$ mg % to $2.5x10^{-3}$ mg % to ashes, Biomass are hard physical work (swimming test) and also had stress-protective, immunomodulating action and anticarcinogenic effect hampered the sarcoma-180 by 33-80% and suppressed quantity of metanes on 43 - 46%.

Introduction

Ginseng (*Panax ginseng* C. A. Meyer, Araliaceae) is a relict plant, but this plant have used in Oriental medicine for more than 400 years. Various publication contain numorous indication of the use of ginseng in the of the most various disease. Yet, it should be noted that Ginseng is not specific remedy for any particular disease. These remedies are named the by Academic N. V. Lazarev the adaptogens (1). Adaptogens medicinal remedies that increase the human body's capacity to adapt oneself to the action of abnomal physical, chemical and other environmental factors. The adaptogen must be non toxic; have not action in norm and to express nonspecifically action to organism in abnomal conditions. Ginseng has been provided as one of the best natural adaptogen (2).

Usually all pepole are in ≪third gtate≫ or status, between the health and ills. Today according to date from the Word of Organization Health, adaptogenic preparations will play a great part in preventive medicine by the year 2000. Ginseng is expensive medicinal plant, which play an important role both now and in the future.

The aerial of Ginseng in Russia are restricted to the Far East. Its natural reserves are very small and in Russia its included in the 'Red book.' Only the technique of isolated cells and tissue of plants can to help deside this problem (3).

It is known that the tissue culture of *Panax L.* receive a wild attention in Russia, USA, S. Korea, Japan and other countries. In 1950 in Moscow in the instilute of physiology of plants Dr. R. Butenko

obtained *in vitro* the cells from various plants including many medicinal ones, among them was Ginseng (4). Today the amount of stains of medical plants has long exceed many thousands species, only some of them con perform the role of industrial stains. Among then Ginseng occupies one of the first places (5,6,7).

Analysis of the patents of USA, Canada, Japan and other countries to allow reveal some substances with high induction of interferon. Its was Ge-organic compunds. In USA, Japan and Gemary these compounds were used as independent substances and as addition to some food products and now its often used as immunomodulating and anticarcinogenic agent (8,9,10).

Materials and Methods

In the 1965 year different strains of tissue culture of *Panax ginseng* C. A Meyer. *P. quinguefolins* L. and *P. japonicus*, C.A. Meyer. have been received on modifications of Murashuge and Skoog Medium (11). In this work was used the strain *P. ginseng* (GCCHP NO. 11 IPhP G-5), received from root 7th years plants from collection Prof. I. V. Grushvitzky.The General Collection Cell Cultures of thigh Plants** IPHP-Institute Plysiology of Plants name Timiryazev K.A. (Moskow)

Table 1. The some ginseng strains selective with Ge-organic compounds

Strain	Author and date of received. Author certif. Patent
Panax ginseng C. A. Meyer GCCCHP* No. 11 IPhP** G-5, received from root 7 years plants from collection Prof. I. V. Grushvitzky.	L. Slepyan et al. 1965. Author certif. 1039963, from 01,12,1981. Author certif. 1123701, from 25,07,1983. Patent R. R. 2058784, from 28,07,1992.
Ginseng selective Lx-13 — 《Panaxel》 GCCCHP* — No. 26.	L. Slepyan et al. 1985. Author certif. 1142295, from 29, 10, 1986. Patent R. F. 2046140, from 08, 07, 1992.

*GCCHP — The general collection cell cultures of thigh plants
** IPhP Institute Physiology of Plants name Timiryazev K. A. (Moscow)

Technology is based on the use of various strain obained with the use of biotechnological methods. The nutritional medium contain macro-and microelements of Murashige and Skoog, sucrose 2,5%; 0.6g/l caseine/hydrolysate; 0,08g/l inozite; 1,0mg/l kinetin; 2,0 mg/l α-naphtylacetic acid without variation all period.

The strains remains stable during all period cultivation in industry from 1985. Cultivation is superficial, wastelss, ecologically clean. Cycle cultivation 25-35 days, temperature 25 ± 10℃ in dark.

Ge-organic compounds - Lx-13-2-carboxiethyl-germanysesquioxan; and Lx-5-1-hydroxigermany-trans-monohydrat. Thes compounds were not toxic (LP_{50}-16-20g/kg), good dissolved in water and have high induction of γ-interferon.

Lx-13-$(O_{1.5}, Ge, CH_2, CH_2COOH)_{n.\ n\text{-}50}$

Lx-5-HO Ge(O, CH_2, CH_2)3 N H_2O)

Methods. The moisture, aishs and contents of extractive substances were defined by methods discribed in Russian Pharmacopoeia XI.

The quantity of ginsenosides was determined by method of Autan *at al.* (13). The phyosterins content defiend by method(14) petin and protopectins contents were determined by method (14) and microelements analysis was carried out by atom-absorption method. The content of Germanium in biomass of selective strains was analyzed by neirono-activation method. For histological studies stndies was used the usual methods.

Results and Discussion

1. Cell development and differentiation long lived *in vitro* strain of Ginseng. There is no doubt today that plant tissue culture (ptc) studies have significantly contributed to our knowledge of plant secondary products. Some scientists still doubt that (ptc) can be developed that are genetically in stable. It is a hard fact that our industry not only require that (ptc) produce large amounts of compounds, as (ptc) system have been successfully developed to study secondary products, so it will be succesfully applied by industry. Although in adequate yield and genetic instability are sometimes significant problems. The real futrue need before industrial application is possible is a better understanding of plant differentiation and the development for innovative bioengineering.

The biotechnology of the plant cells can not understand without knowing from what cells consist of the strain-producer. In this connection we studied the histological characteristics of the strains in the process of its cultivation. After the first 2-3 years passages the biomass of the strains of Ginseng was represented by this-walled parenchmatic and meristematic cells with a large nucleus often with 2 or 3 nucleoli.

The part of meristematic cells begins to grow extension and conversion to prosenchimatic ones. At the same time the part of these prosenchimatic cells lenghtening by hundreds times, lose the nucleus, cytoplasm and obtained the secondary bluge of side wall. Thus the prosenchimatic cells transformed to conducting elements of xylem-tracheids or hydrocytes. It is very interesting, that after first the 10 years recultivation we can see usefully rare individual tracheids among the parenchimatic cells. Its have only sprial or rack bulge pores. After the 20 years of recultivation we can see many typical tracheids with ring-shaped and bordered pores. At the same time the population of parenchimatic cells survive actively divided by periclinal partitions and form the chains of the parenchimatic cells. This

process are very synchronous. To know that such type of divided the cells and the tracheids with bordered pores are characteristic only of the representatives of Angiosperm.

This is a new pathway of histogensis of meristematic cells of higher plants: from a meristem to prosenchimatic cells and then to tracheids with bordered or simple pores. It is clear, that only under the conditions *in vitro* when a cell has to find and realize pathway for quickly growth this way is the most simple.

Thus, the parenchimatic cells of Ginseng under the conditions of culture *in vitro* to pass on the pathway of phylogenically more ancient histological differentiation. This is a typical example when onlogenes of cells repeat its phylogenes but its more ancient type.

Another feature of histogeneis of long lived cells all thes strains are the some prosenchimatic cells become to mechamical fibers libriform type. At conclusion we can be mark, that only due to a close intercellular contact as a result of the subcultivation very long time, just this type of histogenesis became feasible.

In such a manner, in result of long time (more than 30 years) of cultivation these stains of Ginseng on constant nutritional medium with invariable physical condition we received the new biological cells system consist off from the chains parenchimal cells with thin external cellulose membrane, which to security not only the constant rapid grow but also the constant metabolism (Tab.2)

The biomass of tissue culture of *P. ginseng* contain off moisture non more 9-9.7%, aish - no more

Table 2. The growth of long lived in vitro cells strains *Panax ginseng*

Day	After 10 years		After 30 years	
Cultivation	wet weight g/l	dry weight g/l	wet weight g/l	dry weight g/l
1	1.5±0.5	0.09±0.01	1.5±0.5	0.09±0.01
6	3.24±0.4	0.18±0.01	4.1±0.3	0.20±0.01
8	5.42±0.5	0.23±0.01	6.2±0.2	0.25±0.01
13	13.95±0.5	0.28±0.01	14.1±0.5	0.31±0.01
21	16.76±0.4	0.38±0.02	17.3±0.3	0.42±0.01
30	20.0±0.3	0.54±0.01	21.0±0.2	0.56±0.01
35	19.6±0.3	0.52±0.01	20.7±0.3	0.54±0.01
40	19.0±0.2	0.51±0.01	20.1±0.2	0.52±0.01
45	18.5±0.2	0.51	19.2±0.2	0.52±0.01

11-13%, extractive substances with water - non less than 45%, whith 40% ethanol no less 40%, more 2% sugars(glucose fructose) 5,4% of starch, 1.5-2% of lipids, 9,8% cellulose, 15.4-17% pectins, 0.8-1.2% phytosterols, 2.5 - 2,0% sum glycosides. For all Ginseng strains have been found the the vaiations in the content of glycosides fraction are correlated with the maximum of mitotic activity of the

cells and are parallel the logarithmic phase of growth. When cells to pass the stationary phase thes substances were not to increase. This fact is very interesting because role the glycosides for the plant cell are not understand to end. Maybe this process is related with the interaction of cells in biological fields appearing during this growth. In this fields worked as feed back regulator as compartmentalization the major biological active substances in cells and its very sensitivity mechanism to their active division.

If we can understand all process differenciation long lived *in vitro* cells, we can better to explain phylogenetical course to development these plants and also understend the biogenesis all products of metabolism.

2. Selective strain Ginseng with Ge-or ganic compounds

Just like pharmacy cannot be oriented only towards one species even of a very perspective medicinal plant and must to searche for new plants, thus the biotechnology of cells and tissue of medicinal strains cannot be depended one strain-producer only. Selective strain of Ginseng with Ge-organic compound was received by recultivation the cells of *Panax ginseng* on the medium with different concentration compounds (Lx-13) and (Lx-5). In the presence of compounds, we look out only those cells which have shown growth similar or more to that of the control group (tab.3)

After 10 passages was selected the concentration Lx-13 and Lx-5 0,1g/l on which the wet and dry

Table 3. Variation of wet and dry biomass *Panax ginseng* after 10 passages with Lx-13

Control medium		Selective medium with different concentration (Lx-13)					
		0.05 g/l		0.1 g/l		0.25 g/l	
wet g/l	dry g/l	wet	dry	wet	dry	wet	dry
20.0±0.3	0.54±0.02	16.55±2.8	0.64±0.02	28.63±0.38	0.78±0.01	13.2±0.5	0.48±0.03

mass was maximum.

We have obtained the cells which are distinguish from initial Ginseng cells in dynamic of growth, morphological and cytological and some biochomical characteristics (Tab 4)

All biomass was white color, formated mainly the parenchymatic cells and characterized by intensive xylem elements as tracheids near the agar layer.

In this interior layer arise many meristematic sites among the parenchimatic cells and we can see the intensive growth of bicmass. In Table 4, we can see the hight mitotic activity 6% and 8% selective strain on 7 and 15 days. After each 5 passages the biomass of these cells was analized for the content of immunoinducors Lx-13 or Lx-5 by neitrono-activation analysis(Tab. 5).

We have concluded that it is the new selective strain of ginseng. The strain is stabilized under recutivation conditions for all that time. The cultivation is superficial, waste-free, ecologically

Table 4. Growth and mitotic activity cells ginseng on the medium with Lx-13 (0.01 g/l)

Days cultivation	Wet mass g/l	Dry mass g/l	Mitotic activity %
1	1.5±0.2	28.73±0.45	0.1±0.01
5	5.67±0.11		0.25±0.01
10	8.89±0.20		0.33±0.02
15	15.43±0.30		0.47±0.01
20	19.57±0.41		0.51±0.01
25	25.47±0.45		0.65±0.01
30	28.63±0.38		0.78±0.01
35	30.68±0.50		0.95±0.02
40			

Table 5. Summary of Characteristics

Strain	Moisture %	Ashes %	Ge to ashes %	$CHCl_3$ fraction %	CH_3OH fraction %	SGF fraction %	Extract by H_2O
Ginseng	9.5%	12.5	-	2.07±2.5	37.8±2.5	2.5±1.2	40.5±3.5
Ginseng-Lx-13		13.0	10×103	3.18	53.2±1.5	>3.5	>48.0
Ginseng-Lx-5		14.0	2.2×103	3.26	48.7±3.5	>3.0	>45.0

Table 6. The contents of some macro- and microelements in biomass of selective strain was distinct from initiate strain of Ginseng

Elements % to ash	Strain	
	Ginseng	Ginseng-Lx-13
Ash	11.0 %	13.0 %
Ag	0.1×10^{-3}	0.5×10^{-3}
Cu	3.0×10^{-3}	5.0×10^{-3}
Fe	0.3	0.5
Ge	1.0	1000.0
Mg	3.0	3.0
Ni	0.5×10^{-3}	0.5×10^{-3}
Zn	20×10^{-3}	50×10^{-3}

pure/Patent of Russia 1982/This strain are named PANAXEL.

3. The some spectrum of the pharmacological action (Bioginseng-Lx-13)

Bioginseng Lx-13 provides a unique combination of properties typical of Ginseng and those of Germanium. But its spectrum of pharmacological effect is larger than that of the Gingeng.

3.1 Bioginseng-Lx-13 improves the animal tolerance to hard physical work (swimming). After 7

days taking the same dose this effect to increase by Bioginseng-Lx-13 on 152%. Bioginseng provided 140% and Eleutherococcus-130% (Table 7)

Table 7. Influence the Bioginseng Lx-13 to duration of swimming of mice

Preparation	The time of swimming the mice (min)	% to control
Single oral dose (0.1 ml/20g)	16.7±1.18	
1. Control	27.28±3.66	100
2. Bioginseng	24.60±3.31	168.7
3. Bioginseng - Lx-13	21.50±1.85	152.1
4. Eleutherococcus		133.0
7-days single oral dose (0.1mg/20g)		
1. Control	16.86±0.74	100
2. Bioginseng	24.4±0.89	144.9
3. Bioginseng - Lx-13	25.77±1.86	152.1
4. Eleutherococcus	21.88±21.88	129.7

Table 8. Influence the bioginseng and bioginseng Lx-13 to duration of swimming after hypodynamia

Preparation	The time of Swimming min (m/m)	% Control
Single oral dose (0.1 ml/20g)		-
1. Intake	16.7±1.18	100
2. Control-hypodynamia	8.08±0.94	240.0
3. Bioginseng - Lx-13	19.45±2.40	221.3
4. Bioginseng - Lx-13 - hypodynamia	17.88±0.96	
7-days single oral dose (0.1/20g)		-
1. Intake	16.87±0.74	100
2. Control-hypodynamia	8.9±0.63	180.0
3. Bioginseng - Lx-13	16.05±1.15	229.6
4. Bioginseng - Lx-13 - hypodynamia	20.43±2.12	

After influence the hypodynamia (20h) on the action of Bioginseng Lx-13 was larger. (Table 8)

In such of manner Bioginseng -Lx-13 to increase the physical efficiency the mice special on phone the hypodynamia or other stress. It may be very interesting our experiments for treatment the preparation for adaptation to hypoxia of brain (Table 9 a,b)

Table 9a. The influence Bioginseng and Bioginseng Lx-13 on the survival the rats to the sharp hypoxia of brain

Preparation (number rats)	Rain of rats (number/days)				Survivor after 30 days		Middle duration of life (days)
	1	3	4	9	number	%	
1. Control (7)	4	-	1	1	1	14.3	6.7±4.1
2. Bioginseng (7)	4	-	1	-	2	42.9	13.4±6.0
3. Bioginseng - Lx-13	1	1	-	-	4	66.7	20.7±4.2
4. Eleutherococcus (7)	4	-	-	-	3	42.9	13.4±6.0

Table 9b. The influence Bioginseng and Bioginseng Lx-13 on the survival of the rats after hypoxia

Preparation (number of rats)	The time of life the rats (min) (number of rats)
1. Control (15)	5.45 ± 0.53 (10)
2. Bioginseng (15)	11.27 ± 1.50 (9)
3. Bioginseng - Lx-13 (15)	12.04 ± 0.91 (9)
4. Eleutherococcus (15)	10.14 ± 0.99 (9)

In such of manner we can conclusion that Bioginseng-Lx-13 have very much ability to raise the stability of animals to circular hypoxia and process antigypoxical effect. In may be explain by its ability to activation all processes in cells of organism. As adaptation Bioginseng-Lx-13 have also protection and medical action on some pathological model as example the insulin depend diabet (Table 10 a,b).We can see the Bioginseng and Bioginseng-Lx-13 to raise the basal content in blood

Table 10a. The preventive action* Bioginseng and Bioginseng - Lx-13 on rats after alloxan diabet (after 40 min after alloxan injection 250 mg/kl 1 times)

5 ml/kl Preparation (number of rats)	Concentration of glucose in blood, mMol/l	Contents of glycogen in liver, g. %
Intact (Normal Rats (13))	9.36±0.68	2.96±0.17
Control (13)	19.43±1.17	0.76±0.12
Bioginseng (15)	13.84±1.01	1.36±0.17
Bioginseng - Lx-13 (15)	10.31±1.02	1.89±0.17

* Prevention action : The preparation to make use 6 days before injection of alloxan

on 72-110 % and to bring down high concentration of glucose on 20~25% and recovery glycogen in liver.

3.2 Bioginseng-Lx-13 has immunomodulating features by increasing the production of endogenous gamma-interferon. It can be used to improve specific and non-specific immunity. When it used on infected mice C57BL which were given at lethal dose of the influenza A/Victory 35/72 (H2N12).

Table 10b. The medical action** Bioginseng and Bioginseng - Lx-13 on rats with alloxan diabet* Prevention action : The preparation to make use 6 days before injection of alloxan

Preparation 5.0 ml/kl (number rats)	Concentration			
	Insulin in blood MKED/ml	Glucose in blood mMol/l	NELA in blood MKEKV/l	Glycogen in liver g %
Normal (15)	52.13±6.5	4.89±0.19	230±13.2	2.23±0.15
	after alloxan injection (130 mg/kg)			
Control (15)	18.74±2.15	7.74±0.36	356.9±20.5	14±0.21
Bioginseng (15)	40.3±4.35	5.84±0.26	248.9±11.8	1.93±0.13
Bioginseng (15)	45.2±1.99	5.21±0.46	257.9±21.5	2.09±0.15

** Medical action : Preparation to make use the 6 days after injection of alloxan

Table 11a. The medical action Bioginseng-Lx-13 and Bioginseng on survival the mice C57BL/6 after contaminate its the lethal dose virus of influenza A/Victory 35/72 (H3N12)

Preparation (number of mice)	General survival		The presurvival on 14 days after contamination	
	Absolute numbers lively	%	Absolute numbers	%
1. Control (52)	16	31	4 (13)	31
2. Ginseng root (56)	23	41	5 (14)	36
3. Bioginseng (58)	15	15	5 (14)	36
4. Bioginseng-Lx-13 (52)	40	77	10 (13)	74

Table 11b. The prevention action the Bioginseng on survival of mice after contamination the lethal dose virus of influenza A/Victory 35/72 (H3N12)

Preparation (number of mice)	General survival		The presurvival on 14 days after contamination	
	Absolute numbers lively	%	Absolute numbers	%
1. LVI-placebo (80)	35	44	5 (20)	25
2. LVI-Bioginseng + Lx-13 (80)	60	75	11 (20)	55
3. LVI-Bioginseng (76)	47	62	6 (9)	31

Bioginseng Lx-13 provided 77 % survival rate. Under the same condition the Bioginseng provides only 41% and Electherococcus up the survival of animal to 50%.

Bioginseng Lx-13 stimulate the production of spool of antibody producing cells (and HBS AOK) and the virus antigen (surface antigen of B1 hepatitis) in murine spleen, exceeding the preparation of Bioginseng 6.3 times.

Bioginseng Lx-13 stimulate the proliferation of β-lymphocytes upon the immunization development of cellular immune system. It can be used to correct secondary immuno-deficiency problems

which are manifested as decrease in cellular immunity.

3.3 Anti-carcinogenic effects have been investigated on next models of inductive tumors: lactic gland, nervous system and kidneys, cervix of the uterus and vagina. Anti-tumors activity has been tested on sarcoma-180 and carcinoma of lungs of Louis.

Adenocarcinoma of mammary gland were induced in rats by single inflammatory injection of N-methyl-N-nitrosourea (MNU) at a dose of 1 mg per gland into the tissues of all 12 mammary glands. The Bioginseng and Bioginseng-Lx-13 were given per os at a daily dose of 0.5 ml per rat for 27 weeks.

The carcinogenesis induced by transplacental administration of N-nitrosoethylurea (ENU) were given orally over year. The administration of the drugs was followed by longer survival of the rate and lower occurrence and/or multiplicity of tumors.

The Bioginseng and control and MNU-groups decreased the incidence and multiplicity of mammary gland tumors at 44% and 62% respectively beginning one week after MNU administration (18).

It has been established, that administration the both preparation on 11 days have shown the lowering of the frequency and the plurality of tumors of the lactic gland by 43% Bioginseng and by 47% Bioginseng-Lx-13.

Only Bioginseng-Lx-13 for certain has hampered the development of the tumor of sarcoma-180 at 65% and has suppressed the increase of carcinoma of lungs by the 11th day and all periods of the lowering of the quantity of metastases by 46%. Clinical test have confirmed that Bioginseng and Bioginseng-Lx-13 are possessed oncoprophilactic and oncotherapeutic activity.

Conclusion

Technology is based on the use of various strains Ginseng received by biotechnological methods from the cells of root *Panax ginseng*. Strain have stable growth and contents of biological active substances after 30 years. We had received the special biological systems, consist of population synchronic divided parenchimatic cells, and very long mechanical fiber libriform type.

The biotechnology of the special strains of ginseng to open the new fundamental base in phamaceutical industry for ginseng new preparation for health.

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