

# Selective Plant Extracts and their Combination as the Nutritional Therapeutic Remedies

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**Abstract:** The article is a survey of some plant extracts that possess ability to restore metabolic disturbances evoked by chronic stress. Chronic stress triggers a number of common illnesses, including depression, chronic physical and mental fatigue, neuroses, cardiovascular diseases, ulceration of stomach and intestine, diabetes mellitus, obesity and alcohol abuse. One of the early consequences of chronic stress is the decrease of functional activity of immune system that reduces resistance against infections, allergies, asthma, autoimmune disorders, rheumatoid arthritis. The initial stages of chronic stress consequences are suppression of immune system, disturbances of hormonal balance, hydrocarbon, lipid, and energy metabolism. Applicability of the extracts from *Leuzea carthamoides*, *Rhodiola rosea*, *Eleutherococcus senticosus*, *Schizandra chinensis* and their combination "AdMax" to counteract the initial stages of chronic stress consequences is considered.

**Keywords:** General adaptation syndrome, Chronic stress consequences, Adaptogenic plant extracts, Nutritional supplement "AdMax", Chronic fatigue, Energy metabolism.

## CHRONIC STRESS CONSEQUENCES

As it is known, many functions of various tissues in the organism, especially endocrine glands, are controlled by division of the brain called hypothalamus. The regulation of functional activity of the body by hypothalamus provides a constancy of the composition of the body's internal surroundings known as homeostasis. External and internal stress factors disturb homeostasis and evoke activation of the stress system. The system consists of the vegetative nervous system, adrenals, pituitary gland and hypothalamus—the key component of the stress system. An activated state of the system is what is known as stress. During stress significant changes in the organism are observed: reducing of synthesis of male and female sex hormones, suppression of thyroid function, increasing of protein catabolism, lowering of fat decomposition, increasing of glucose synthesis and suppression of immune system [1].

In contrast to short-term action of stressors, which evokes quickly passed stress, long-term action of stressors does not allow the stress system to return to normal. That leads to exhaustion of the system reserves to adaptive response to chronic stressor's influence. Chronic stresses can cause various functional disturbances and diseases. The most characteristic common illnesses triggered by chronic stress include chronic physical and mental fatigue, neuroses, depression, cardiovascular diseases,

ulceration of stomach and intestine, diabetes mellitus, obesity and alcohol abuse [2].

One of the early consequences of chronic stress is decrease of functional activity of immune system. That reduces the resistance against various infections, inflammatory lung disorders, allergies, asthma, autoimmune diseases, rheumatoid arthritis and decreases body's ability to repair tissue damages. Chronic stress aggravates already existing diabetes mellitus both type, increases hyperglycemia and hypercholesterolemia [2]. Initial stages of most chronic stress consequences are suppression of immune system, disturbance of hormonal balance, hydrocarbon, lipid, and energy metabolism.

In accordance with well-established theory of stress by Hans Selye, the response to stress factor action is so-called "general adaptation syndrome" [3]. The term "adaptogen" designates a natural substance that is able to increase nonspecific resistance of the organism against action of various stressors and thereby to promote adaptation of the body to stressful conditions. It is suggested that adaptogen's action directs to recovery of functional changes evoked by stress.

At the last time molecular mechanisms of stress-protective activity of adaptogens are under the study [4]. Some data indicate that active compounds of adaptogenic plant extracts act on body cells on the level of hormonal receptors and membrane proteins of corresponded signaling pathways [5]. Biological effectiveness of concrete plant compound is determined by level of its affinity to the responsive membrane protein.

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It is important, that most of biologically active compounds isolated from adaptogenic plant extracts demonstrate lesser biological effect than the effect of whole extract. The reason for that is synergistic action of the extract constituents. Presence in the plant some adjuvant compounds can enhance the activity of the compounds actually responsible for the biological effect. Some other mechanisms of synergistic interactions of the extract constituents can also determine biological activity of the extract [6, 7].

The adaptogenic properties of the extracts from four plants, that have been undergone most careful and rigorous testing by scientists and physicians, are described below. Extracts from these plants are constituents of the nutritional supplement "AdMax".

### ***Leuzea carthamoides* Extract**

*Leuzea carthamoides* (Will.) Iljin., synonyms: *Rhaponticum carthamoides*, *Maral root* belongs to the *Compositae* family of plants and is a rare endemic species. It is herbal perennial plant reaching 180 cm of height. *Leuzea* grows on the mountain slopes in a limited area of southern Siberia (Altay, Sayani); it does not exist as a wild-growing plant in other regions of the world. The history of *Leuzea* as a medicinal plant begins in ages past when hunters noticed the unusual behavior of a local variety of noble deer known as *Maral*. At the time of mating, when males fight each other and need to restore their strength, stags dig out and eat *Leuzea* roots. Local healers discovered that consumption of dried *Leuzea* roots decoct by man also helped him recover from fatigue and increase his sexual potency. The plant was thereafter named "Maral root" and now it is the official common name of *Leuzea*.

Scientific studies of *Leuzea*'s influence on the human organism began in Russia in the 1940's, during World War II, when the country had a needed medication to help restore strength and stamina of its soldiers. The study is prolonged to the present time. It was established that ethanol/water extract of dried *Leuzea* roots contains ecdysteroids, flavonoids and its glycosides, lignans, lactones, triterpenes, alkaloids, polyenes, organic acids and some other [8, 9] as well as a number of yet-to-be-identified compounds.

Numerous experiments and clinical trials reveal that *Leuzea* root extract:

- increases physical performance and endurance [10];
  - increases skeletal muscles mass [11];
  - restores humoral immunity decreased as a result of intensive training in athletes [12];
  - prevents stress-induced sleep disorders [13];
  - improves conducting of nervous impulses in central nervous system [14];
  - elevates sexual function in animals and men [15];
  - promotes restoration of liver tissue under hepatitis [16];
  - improves learning and memory in animals [17];
  - positively influences on cardio-vascular system [18].
- Among various active compounds of *Leuzea* root extract, the very important is ecdysterone (20-hydroxyecdysone), a polyhydroxylated sterol belonged to ecdysone group. The function of this compound in the plant is unknown. Interestingly, that ecdysterone presents also in some insects and crustaceans but absent in vertebrate animals or in humans. In insects and crustaceans ecdysterone plays a role as the hormone participated in regulation of growth and development. In these organisms ecdysterone presents in trace quantities: only 2 mg of ecdysterone can be isolated from 2 tons of crabs [19].
- Because ecdysterone was not known to exist in mammals and humans, scientists at first did not pay attention to men as a subject for research of ecdysterone activity. Later, scientists established that ecdysterone is physiologically active with respect to mammalian and human cells. It has been shown that ecdysterone:
- activates protein synthesis in skeletal muscles and heart [8, 20];
  - increases adenosine triphosphate (ATP) synthesis in muscles [21];
  - stimulates production of erythrocytes [22];
  - decreases hyperglycemia in animals with experimental diabetes [23];
  - reduces of cholesterol level in the blood stream [24];

- decreases activity of triglyceride lipase [25];
- provides protective action against experimental atherosclerosis in rabbits [26];
- activates synthesis of acetylcholinesterase in the brain, an enzyme involved in regulation of nerve impulse transmission in cholinergic neurons [27];
- activates synthesis of glutamate decarboxylase, an enzyme involved in synthesis of neurotransmitter GABA in the brain [28];
- possesses immuno-modulating action [29].

The mechanism of ecdysterone action is not known precisely, but existing data indicate on some similarities of its action mechanism with that of human steroid hormones [30, 31]. This means that ecdysterone interacts with steroid hormone receptors of human cells. Human endogenous hormones have, however, an advantage over ecdysterone because of their higher affinity and specificity to the human hormone receptors. When human steroid hormones are produced in sufficient quantities in the body, ecdysterone does not evoke an effect because it can't compete with endogenous hormones for the receptors. But when there is a deficiency in the body of its own hormones, ecdysterone can bind to unoccupied steroid hormone receptors, replacing the missing endogenous hormone. Probably also, that ecdysterone binds to some cellular membrane proteins involved in corresponding signaling pathways.

In athletes, repeated physical activity triggers an adaptive synthesis of oxidative enzymes, contractile proteins in muscle cells and the growth of new muscle capillaries. This occurs with the participation of testosterone, which activates the genes controlled protein synthesis. During exhaustive physical exercises, the testosterone concentration in the blood stream drops. In this case ecdysterone can become a substitute for the missing testosterone, displaying its anabolic activity and promoting the adaptation to physical stress.

Especially one should note the significance of anabolic effect of *Leuzea* root extract and its constituent ecdysterone for prevention of protein catabolism characteristic for the elderly. It was established that since the fourth decade of life synthesis of muscle and mitochondrial proteins begins to drop and catabolism of the proteins begins to predominate [32]. Amount of muscle protein myosin

heavy chain (isoform IIa) decreased by 38% from young to middle age and further decreased by 50% from middle to old age [33]. It was showed also that mitochondrial ATP production declined with advancing age [34]. It is suggested that reduced ATP production can be base for reduced muscle protein metabolism, which requires energy [32]. As a result of this loss of power, physical activity, skeletal muscle mass is observed with advancing age. *Leuzea* root extract counteracts these processes [11, 21].

Strenuous physical activities and sports cause a dramatic increase in oxygen uptake by muscles and some other tissues. As a result oxidative stress is raised and  $H_2O_2$  is accumulated in these tissues. Hydrogen peroxide is formed as a by-product of energy metabolism and is harmful in excess quantities because it can interact with lipids of cellular membranes, proteins and DNA, disrupting the functions of various tissues and even trigger of cancer arise. Catalase is an enzyme, which decomposes  $H_2O_2$  and prevents oxidative damages in the cell. Ecdysterone is capable to increase catalase activity [35] and thus can counteract hydrogen peroxide accumulation during physical stress.

It was showed recently that *Leuzea* root extract contains some other ecdysteroids [36] but their content in the extract is significantly smaller in comparison with ecdysterone content and their bioactivity is poorly studied. Interesting compound of *Leuzea* root extract is hydroxylated polyphenolic compound stilbene [37]. It was recently established that similar compound called resveratrol (3,5,4' – trihydroxystilbene) effectively prevents fat deposition and increase insulin sensitivity in animals on a high-calorie diet [38], that allows decrease overweight without caloric restriction.

*Leuzea* root extract contains also other biologically active compounds belonged to bioflavonoids and their glycosides. Bioflavonoids are well known as active components of non-enzymatic antioxidant system in cells. Besides, some of them possess also estrogenic activity. However affinity of the bioflavonoids to estrogen receptors is low in comparison with endogenous estrogens [39]. Therefore the bioflavonoids can interact with estrogen receptors in conditions of insufficiency of endogenous hormones that is usually observed during stress.

*Leuzea* root extract and ecdysterone don't evoke any toxic effects during extended period of their introducing in various animals.  $LD_{50}$  for mice upon

intraperitoneal administration of ecdysterone is 6.4 g/kg [40] that is abnormal mega dose. Numerous and prolonged clinical observations evidence about absence of harmful effects of *Leuzea* extract intake by humans.

### ***Rhodiola rosea* Extract**

*Rhodiola rosea* (L.) is a perennial grassy plant that belongs to the *Grassulaceae* family. It is also known by the common name "Golden root". *Rhodiola* is a rather polymorph plant whose anatomical structure and content of biologically active compounds can vary from region to region. In Russia, *Rhodiola* grows in mountainous areas in southern Siberia (Altay, Sayani, Tuva) as well as on Sakhalin island and Kamchatka. The plant regenerates very slowly and therefore the collection of wild *Rhodiola* in Russia is limited.

The roots of *Rhodiola rosea* have an unusual reddish golden color. The plant, however, was not given the name Golden root simply because of its root color. It has long been a highly valued plant because of its ability to restore strength and to preserve health. On his wedding day, the Siberian groom traditionally received Golden root as a sexual stimulator. Chinese emperors sent expeditions to the mountains of Altay to search for the plant while local inhabitants tried to keep the locations of the plant secret.

Scientific studies on Golden root began in Russia in the 1960's after botanists had identified it in the mountain forests of Altay as *Rhodiola rosea*. Different groups of substances have since been detected in the water/ethanol extract from its roots, such as sterols, flavonoids, organic acids, phenylalkanoids, monoterpedoids. 10 phenylpropanoid glycosides were identified, including salidroside, rosin, rosavin, rosarin and some others [41]. Not all compounds have yet been identified.

One of identified compounds possesses most of the physiological activity characteristic of the plant. It was identified as p-tyrosol glycoside called salidroside. Its content in *Rhodiola* root is approximately 0.2%. The aglicone part of its molecule is structurally close to dihydroxyphenylalanine (dopa), a precursor of catecholaminergic neurotransmitters. It has been experimentally demonstrated that salidroside activates the transmission of nerve impulses in catecholaminergic synapses of the brain [42]. It has been shown also that psychological stress and intensive physical exercise significantly suppress

hypothalamic-pituitary-gonad axis, and that salidroside has protective effect on the neuro-endocrine system [43]. Salidroside possesses neuroprotective [44] and cardioprotective [45] effects. Salidroside enhances glucose uptake in skeletal muscles and insulin sensitivity [46]. However, the action spectrum of salidroside is only part of more wide action spectrum of whole extract from *Rhodiola* roots. In some tests physiological effectiveness of isolated salidroside is significantly less than that of the whole extract [42].

Animal testing shows that *Rhodiola* extract increases duration of exhausting swimming for 24% and elevates synthesis of ATP in muscles [47, 48]. In humans intake of *Rhodiola* extract improves endurance exercise capacity [49]. *Rhodiola* extract increases activity of the cytochrome system and some other oxidative enzymes. It also prevents a reduction of tissue concentrations of glutamic and aspartic acids that play important roles in muscle protein metabolism. Structural changes of mitochondrial membranes in muscle fibers under physical stress, as detected by electron microscopy, are significantly less pronounced when *Rhodiola* extract was used prior to exercise [42].

During hard physical exercises energy metabolism is changed not only in muscles but also in the brain. Concentrations of ATP, creatine phosphate and glycogen in brain tissues drop. The introduction of *Rhodiola* extract before intensive exercise supports almost the initial levels of those compounds significantly longer, thereby sustaining the energy supply to the brain. This is most likely the result of activation of oxidative phosphorylation processes under the influence of the extract [42].

*Rhodiola* extract possesses anti-hypnotic and anti-toxic properties. Administration of the extract reduced the duration of sleep caused by barbital in mice. Pretreatment of mice with 0.1 ml of *Rhodiola* extract once a day for ten days increased LD<sub>50</sub> of 40% ethyl alcohol from 24.1 to 56.2 ml per kilogram of body weight (42). It was shown also that in mice *Rhodiola* extract reduces the toxicity caused by cancer chemotherapy drug cyclophosphamide [50].

Positive effect of *Rhodiola* extract was observed in patients with neuroses, accompanied by lowering attention and memory [51]. *Rhodiola* extract increases the ability to perform intellectual work for prolonged periods of time, especially if such work requires a high degree of concentration [52-54]. It was established also in animal experiments that *Rhodiola* extract possesses

modulating effect on content of catecholamines and serotonin in the brain [55]. Rhodiola extract enhances level of serotonin (5-HT) in hippocampus in depressive rats, induces neural stem cell proliferation at hippocampus to return to normal level, repairing the injured neurons [56]. No any evidences have been published about harmful effects of Rhodiola rosea extract intake in clinical practice.

### ***Eleutherococcus senticosus* Extract**

*Eleutherococcus senticosus* (Maxim) is known also as “Siberian Ginseng” because its influence on the human organism is to some extent similar to that of the well-known Chinese Panax Ginseng. Both of these plants belong to *Araliaceae* family, but morphologically they are two completely different plants: Panax Ginseng is a comparatively small herb, while *Eleutherococcus* is a perennial bush 2-5 m in height. *Eleutherococcus* grows in the Far East area of Russia as well as in northeastern China, northern Korea and Japan.

The adaptogenic properties of *Eleutherococcus senticosus* roots were first revealed in 1960's and extensively studied in pharmacological laboratory of I. Brekhman at the Far East Center of the Russian Academy of Sciences [57]. The physiological action of *Eleutherococcus* extract is determined predominantly by the presence of seven different glycosides called eleutherosides, aglycones of which differ from one another [58]. Other bioactive glycoside is syringin, which is not characteristic only for *Eleutherococcus*. Individual eleutherosides isolated from *Eleutherococcus* extract as well as their mixture demonstrate, however, lesser wide action spectrum than the whole extract [59]. That indicates on the presence of other bioactive compounds in *Eleutherococcus* extract.

A number of observations concerning of biological effects of *Eleutherococcus* roots water/ethanol extract have been published [60, 61]. Most significant effect of *Eleutherococcus* extract is activation of some components of immune system. As it was shown in mice, oral administration of *Eleutherococcus* extract elevates amount of immunoglobulins in the blood serum [62]. In clinical study it was established that the extract administrated orally drastically increase the number of immunocompetent cells especially T-lymphocytes [63]. It was shown that *Eleutherococcus* extract influences the synthesis of cytokines by macrophages in human blood and acts not as immunostimulator, but rather as immuno-modulator [64].

*Eleutherococcus* root extract possesses ergogenic activity improving physical exercise performance [65-69]. The extract improves human sperm mobility in patients with asthenospermia [70]. It was shown that eleutherosides and syringin from *Eleutherococcus* decrease plasma glucose level [58], enhance glucose utilization and glycogen synthesis in diabetic rats [71]. *Eleutherococcus* and Rhodiola extracts increase stress resistance and lifespan in the nematode *C. elegans* [72]. In the experiments with cultured cortical neurons it was found recently that *Eleutherococcus* extract inhibits neurite atrophy and synapse loss damaged by amyloid beta(25-35) [73]. This finding is interesting from the viewpoint of searching for potential drugs against neurodegenerative diseases. It was revealed also that intake of the extract improves mental health and quality of life in the elderly [74]. *Eleutherococcus* extract is not toxic in usually used doses during prolonged period of time.

### ***Schizandra chinensis* Extract**

*Schizandra chinensis* (Turcz., Baill), the member of the *Schizandraceae* family, is a perennial wood-like liana. It is endemic plant of eastern-Asiatic countries. It grows in the easternmost regions of Siberia, in China, Japan, and Korea. Roots, stems and leaves of *Schizandra* have a strong lemony smell that is why the plant is known in Russia as “Limonic”. The fruit of the plant is main material, which is used for obtaining of water or water/ethanol extracts. In Japan *Schizandra* fruit is called “Hoku-gomishi”, in China – “Wuweizi”.

*Schizandra* is a traditional medicine in China since ancient times. Inhabitants in those regions of Siberia where the plant grows have used its berries for centuries to restore power after hard physical work. The berries are also traditional source of juice, while the liana bark and leaves are tea substitutes. Scientific studies of *Schizandra* fruit biological effects began in Russia in the 1960's [75]. A number of adaptogenic effects of *Schizandra* fruit extract have been observed by Russians researchers, such as protective action against various stress factors and increasing of physical workability [76]. Unfortunately these works were not published in western scientific journals at that time.

The first compound that possesses adaptogenic properties was isolated and its molecular structure was established by Russian scientists in 1962 [77]. This compound has been called schizandrin and turned out to be a lignan with a dibenzocyclooctadiene skeleton.

Five other compounds with spectral properties similar to those of schizandrin have been detected and named schizandrins [78]. Japanese scientists established structures of these five compounds in 1978 and called them gomisin A, B, C, F, G. Their structural skeleton is also based on dibenzocyclooctadiene [79]. In scientific literature these compounds more often are called "schizandrins".

Biological activity of isolated schizandrins is determined, in great extent, by their scavenging effect on active oxygen radicals [80-83]. Besides anti-oxidant activity, it was showed that in liver of mice poisoned by carbon tetrachloride (CCl<sub>4</sub>) some schizandrins enhance mitochondrial glutathione redox activity, which decreases hepatotoxic effect of CCl<sub>4</sub> [84]. Gomisin A promotes liver regeneration after partial hepatectomy [85]. Schizandrin possesses anti-inflammatory activity [86], protects myocardium [87] and brain tissue [88] against ischemia injury in mice, reduces hepatic cholesterol and triglyceride levels in mouse model of hypercholesterolemia [89]. Some schizandrins act as platelet-activating factor (PAF) antagonists [90]. Schizandra extract is not toxic in reasonable doses. LD<sub>50</sub> for mice is 10 g/kg that exceeds usually used doses in thousands folds. Isolated schizandrins demonstrated even lesser toxicity than Schizandra fruit extract [76].

Numerous experimental researches and clinical observations described above argue that extracts from *Leuzea*, *Rhodiola*, *Eleutherococcus* and *Schizandra* possess ability to restore a various metabolic disturbances, which are often evoked by stress. Proprietary blend of dry extracts from these four plants entitled "AdMax" is manufactured by Nulab, Inc., Clearwater, FL 33765, USA, ([www.nulabinc.com](http://www.nulabinc.com)). Some published results obtaining upon researches of AdMax biological activity briefly described below.

### **ADMAX Influence on Immune System**

The influence of AdMax on immunity of ovarian cancer patients was studied in Cancer Research Center in Moscow [91]. 28 patients with stage III-IV epithelial ovarian cancer were treated once with 75 mg/m<sup>2</sup> cisplatin and 600 mg/m<sup>2</sup> cyclophosphamide. Peripheral blood was collected before the chemotherapy and 4 weeks after that. Subclasses of T, B and NK lymphocytes were tested for in the blood samples: CD3, CD4, CD5, CD7, CD8, CD11B, CD16, CD20, CD25, CD38, CD45RA, CD50, CD71 and CD95. Immunoglobulins G, A and M concentrations were also determined.

Changes were observed in following T cell subclasses: CD3, CD4, CD5 and CD8. In 9 women who took AdMax (270 mg a day) for 4 weeks following the chemotherapy, the mean number of the four T cell subclasses was increased in comparison with the mean number of the T cell subclasses in patients who did not take AdMax. In patients who took AdMax, the mean amounts of IgG and IgM were also increased. The obtained results suggest that the combination of extracts from the adaptogenic plants may boost the suppressed immunity in ovarian cancer patients who are subject to chemotherapy. Some side effects observed in patients as a result of the chemotherapy such as chronic fatigue and depressive mood were mitigated in patients who took AdMax following the treatment. The obtained results are consented with the data about influence of some AdMax constituents on cell-mediated and humoral immunity [12, 59, 62, 63].

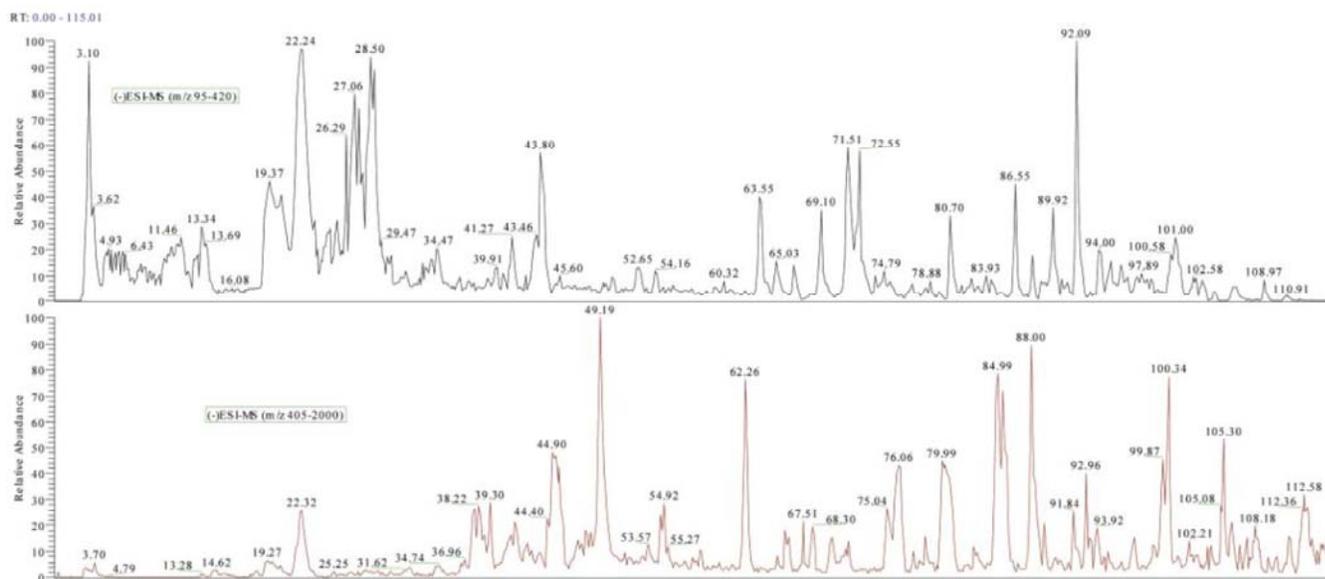
### **Enhancing of Sexual Function by AdMax**

A double-blind, randomized placebo-controlled study of influence of combined preparation AdMax with some additives on male sexual function was carried out [92]. 40 individuals received the study preparation and 20 participants received placebo during 7 days. All participants completed The International Index of Erectile Function [93] prior and after the trial. The Index includes 5 characteristics of sexual function. Recipients of study preparation had vastly favorable responses. In particular, value score of erectile function was enhanced from 11.5 to 22.7 ( $p < 0.005$ ) and intercourse satisfaction from 5.6 to 11.1 ( $p < 0.005$ ), i.e. in fact these characteristics of sexual function were increased of two times. Because reducing of synthesis of sex hormones is one of the stress consequences [1], AdMax or its modification may be used as a remedy for enhancing of reduced sexual function.

### **HPLC/MS Characterization of AdMax Composition**

AdMax composition was analyzed via reverse phase gradient C18 HPLC/ESI-MS utilizing negative ionization with two MS scan ranges [94]. Used instruments: HPLC – Agilent 1100; Mass Spectrometry – ThermoFinnigan LCQ in electrospray ionization (ESI) mode. Base peak ion chromatogram of AdMax composition is presented below Figure 1.

As it is seen the chromatogram registers more than 80 highly abundant peaks and many minor peaks. Abundance of each peak characterizes the amount of corresponded compound. This chromatogram



**Figure 1:** HPLC/ESI-MS registered base peak ion chromatogram of AdMax composition upon negative (-) ionization with two scan ranges (m/z 95-420 and 405-2000).

demonstrates complexity of AdMax composition. The chromatographic profile is characteristic for AdMax and is used as a fingerprint for quality control of AdMax composition.

### AdMax Capability to Modulate Gene Expression

Cultured human fibroblasts (MRC5) have been used for study of AdMax influence on human gene expression [94]. AdMax was administered into culture medium at concentration of 3  $\mu\text{g}/\text{ml}$  and the cells were incubated during 16 hours before RNA collection from the cell lysates. Whole-genome microarray analysis was performed using Affimetrix GeneChip Human Genome U133 Plus 2.0 array that allow one to measure expression levels of the whole human genome. Comparison gene expression levels into control and AdMax-treated cells were carried out with using Affimetrix software (GCOS).

As the result of AdMax-treatment 67 genes changed their expression more than 2 fold ( $P < 0.05$ ). Genes modulated by AdMax are involved in a variety of cellular processes including protein, nucleic acid, lipid and carbohydrate metabolism, regulation of transcription, signal transduction, response to stress and stimulus, and some other.

The obtained results give evidence about ability of AdMax to modulate expression of number of human genes in cultivated cells. These data promote understanding of diversity of described above biological effects of the adaptogenic plant extracts.

In connection with AdMax ability to counteract physical and mental fatigue as a consequence of stress and restore endurance performance in athletes it is interesting to note significant increase of expression level of gene PANK2 in the cells upon AdMax influence. Expression level of the gene was increased by 2.3 fold ( $P = 0.004$ ) as compared to control cells [94]. PANK2 encodes a mitochondrial enzyme pantothenate kinase 2, which activates coenzyme A (CoA) biosynthesis [95, 96]. CoA plays a key role in energy metabolism. Activation of CoA biosynthesis by AdMax is one of the possible mechanisms due to which AdMax counteracts energy insufficiency evoked by chronic stress. Decrease of pantothenate kinase activity is also associated with neurodegeneration [97]. In the elderly neurodegenerative diseases, such as Parkinson's and Alzheimer's diseases, are caused, with high probability, by impairment of neuronal energy metabolism [98-103].

As a result of the study increase of expression level of gene IGH1 by 2 fold ( $P = 0.011$ ) upon AdMax treatment was also revealed. IGH1 controls the binding of immunoglobulines to antigens that provides immune system response to infection [94]. Increase of IGH1 expression upon treatment with AdMax may contribute to restoration of immune system activity decreased by chemotherapy in cancer patients [91].

As described in the review, extracts from the four above mentioned plants possess a number of biological effects. This can be explained by the multicomponent composition of each plant extract. Further research is essential for establishing

biochemical mechanisms of the effects of individual compounds of the extracts. It will allow us to design preparations of the plant origin comparable in specificity and efficiency to pharmacological formulations.

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