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REVIEW ARTICLE

EFFECTS OF HERBAL SUPPLEMENTS ON THE IMMUNE SYSTEM IN RELATION TO EXERCISE

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Athletes who undergo strenuous exercise, especially in endurance sports, frequently use herbal supplements in order to have a better performance. In this review we try to find out if the most common herbal supplements (Echinacea, Rhodiola, Ginseng) are effective in the empowerment of perfomance or in the modulation of the immune system. It seems that the prevalent effect is adaptogenic rather than ergogenic, with a better tolerance of the exercise induced stress, related to enhancement of the whole immune system and decrease of the oxidative damage.

During endurance many different types of exogenous substances [1], called supplements, with different mechanisms of action, are used. Generally they use their ergogenic action, that is the enhancement of the whole psychophysical performance or, lastly, their adaptogenic action, which aims to improve the psychological and physical endurance to environmental stress, through different physiological mechanisms, among which we could consider the enhancement of the immune function.

However, in the case of the herbal supplements, since their effect on the human organism is caused by various active principles in different combination, it becomes more difficult to evaluate clinically the balance between benefits and risks.

Purpose of our study was to examine with a review of the international literature the last scientific findings about efficacy and clinical safety of the most common herbal supplements, (Rhodiola rosea, Echinacea purpurea, Panax ginseng), especially as to the activity of the immune system in subjects who undergo to stress from a strenuous exercise.

As to the Rhodiola rosea, for example, many authors [2], especially from North and East Europe, refer interesting properties, both adaptogenic and ergogenic [3] even in chronic fatigue syndrome [4]; besides, it seems to be able to enhance the cognitive function and reduce the mental fatigue [5].

Rhodiola rosea is a plant from the family of Crassulaceae, which grows in the cold lands, particularly in the Arctic areas. From a molecular point of view, these properties should be related to the action of the extract of this plant (mainly the rosiridin), which inhibits [6] the monoaminooxydase A and B, increasing so the levels of serotonin and dopamine, with positive effects on the neurotransmission, particularly in the so called "circuit of pleasure", which links the medial prefrontal cortex to anterior cingulate cortex, amygdala and other limbic and mesencephalic structures, with positive effects on the mood and on the psycho-physical performance. Both in human and in rats it has been shown an improvement of the performance in endurance activity with this supplement [7].

In addition to this, it has been demonstrated its efficacy in patients with depression [8] and in senile dementia. The same plant contains also other important active principles in its rhyzoma, such as terpenic essential oils (overall

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the geraniol and its oxydated metabolite, the rosiridrol), flavonoids and proanthocyanidins, quercetin, gallic acid, chlorogenic acid, kaempferol [9]: these substances have strong antioxidant activity and so could be responsible for the adaptogenic action of Rhodiola [10].

In an experimental study [11] Rhodiola was given for four weeks to fourteen athletes, who underwent a cardiopulmonary test and some blood tests; it resulted that Rhodiola rosea did not modify the maximal heart rate, the Borg score for fatigue, the maximal oxygen uptake (VO2max, index of aerobic power) and the time of the test, but there was a statistically relevant decrease in the level of fatty free acids; the oxidation status of the blood and the inflammatory parameters did not vary; blood lactate and the level of creatine kinase were significantly lower in treated subjects than in the control. From these aspects the authors deduce that this supplement can be adaptogenic as it improves the tolerance to stress of the subject, but the effective activity on the immune system has been not explored.

The review of Kucinskaite [12] seems to confirm not only the ability to increase the endurance and improve the psycho-physical performance, but also antitumoral properties as to hepatocarcinoma, so a direct or indirect enhancement of the NK (Natural Killer) cells.

Indeed [13] another study shows an immune system stimulation from Rhodiola, mediated by the increase of IL-6 and TNF-α and the up-regulation of the nuclear translocation of pI-Kb and of the transcription of the NF-Kb; besides there is an increase of production of nitric oxyde in response to lipopolisaccharide.

It was shown also the efficacy of Rhodiola on the T-helper lymphocites, particularly on Th1 through the increase of IL-2, and on Th2 through [14] the increase of IL-4, IL-6, IL-10. Another study evidences its efficacy in improving the neuro-hormonal response to the stress (ACTH, cortisol, tyroxin); it also increases moderately the basal level of β-endorphin and decreases their level after the stress of exercise.

Another herb with immunostimulating properties, perhaps more known, is Echinacea (coneflower), a gender of herbaceous plants of the family of the Asteraceae, coming from North America, which includes nine species, among which the most famous is purpurea. The root of coneflower has cicatrizing, antiseptic and healing properties. There are a lot of studies that show the ability of the dry extract of Echinacea to ameliorate the immune defense against viruses and bacteria. In fact its principles are active on lymphocytes. Particularly, the immunostimulating action expresses itself as an increase of the phagocyte activity of macrophages and leucocytes, so making the organism more resistant to the attacks of pathogens. Echinacea is very effective on cold syndromes: the EMEA has approved the use of extract of flowers of Echinacea for the prevention in short time and the treatment of cold.

This is of considerable importance for endurance athletes, since it has been shown that exhaustive endurance performances like marathon expose the athletes to frequent infections of the upper airways [15].

In a study [16] a selective efficacy of this species was evidenced in the stimulation of the production of the enzymatic protein NOS (nitric oxide synthetase) in the macrophages rather than in the stimulation of secretion of Interpheron type I, increasing their antiviral activity.

This activity appears relevant in athletes who undergo a strenuous exercise, as the same author [17] reports. As to the interaction with physical exercise, Senchina et al. [18] observed a stimulation of production of IL-1 β, TNF e IL-10 in the mononuclear cells of human blood after administration of Sanguinaria canadensis ed Echinacea tennesseensis, in response both to a graduated test till VO2max, and to 90 minutes of cycling at 85% of ventilatory threshold. In the control, the VO2max test did not determine inhibition of the production of these cytokines, while the other test increased their production, except for IL-10.

In another study [19] examined the different herbal preparations of the traditional Chinese medicine base on Echinacea, that all show immunomodulating activity with a common mechanism of stimulation of at least one cytokine among IL-4, IL-6, IL-10, TNF and IFN-γ. As to the specific molecular action of Echinacea, the study of Benson [20] is very interesting, since it underlines the prevalent effect on humoral immunity and, on the other hand, evidences different actions as to part of the plant used. For example, the extract of the root of coneflower, rich in polysaccharides, stimulates the expression of MHC II, CD86 and CD54, receptors of the dendritic cells, while the extract of the leaf, rich in alchilamide, inhibits it. IL-6 and TNF-α are increased by the root, but not by the leaf; besides, if both stimulate the uptake of ovalbumin in vitro by the murine dendritic cells, only the extract of the leaf is able to inhibit the enzymatic activity of COX-2 and the antigen-specific activation of the naive T lymphocytes CD4+, exhibiting so a more immunosuppressive than immunostimulating action.

More, the chromatographic analysis made by LaLone [21] has detected an action of inhibition of production of PGE2 and nitric oxide in the macrophages of mouse by ketonic compounds and alchilamide contained in Echinacea purpurea, angustifolia, tennesseensis e pallida.

Another very important herb in this field is Panax ginseng, which name derives from the Greek παν □κέια (all diseases) and the Chinese rènshēn (plant of the man). It grows up in North and East Asia (especially Korea,

Northern China and Eastern Siberia) and in North America, typically in cold areas. Panax contains ginsenosides, while the Siberian species (Eleutherococcus senticosus) contains eleutherosides.

Since thousands of years this plant has been employed with different aims: to increase the physical endurance and the ability to recover after a strenuous exercise; to optimize the blood little circulation; to enhance the memory and the psychical resistance to environmental stresses, reducing neurosis; to empower the immune defense, preventing many diseases.

It contains a high quantity of invigorating active ingredients: ginsenosides (chemically complex compounds), saponins with triterpenic structure, all group B vitamins (of which 0.01 to 0.1% colin, a human body substance which helps controlling blood pressure, lowering and thus regulating it), Vitamin C, A, E, K, folic acid, essential oil (0.05%), peptides, pollins, saponosides, all essential amino acids, minerals and trace elements (sodium, potassium, magnesium, sulphur, phosphorus, iron, zinc, cobalt, manganese – a powerful anti-asthenic, alluminium, copper, germanium, silicon, vanadium and different other micro-elements), enzymes (amylase, glycolate oxidase, phenol), polyunsaturated fatty acids (oleic, phytosterols, sesterpenic, stiroleic, oleanolic); organic acids, nucleic acids bases and nucleosides: Adenine, Guanine, Uracil and Uridine; phytosterols: Campesterol, beta-sitosterol, Stigmasterol; estrogen and androgen-like substances: Estriol, Estrone, beta-estradiol; starch, mucilage, tannin, oil and resin. As already mentioned, one of the major Ginseng properties is the capacity to reduce stress damage after exercise. A study by Hsu CC [22] measured plasmatic concentration of creatine kinase (CK) and lactate and highlighted a considerable reduction in concentration in the subjects who assumed Ginseng, whereas VO2max did not improve. Reduction in plasmatic CK could be a consequence of ginseng efficacy in decreasing damage to muscular cell membrane after physical exercise. Kim SH et al.[23] studied the effects of Panax ginseng extract (PGE) on lipids peroxidation and on scavenger enzymes induced by acute exaustive exercise in sedentary man. Malondialdehyde (MDA), catalase (CAT), and superoxide dismutase (SOD) have been assessed and resulted considerably high. Such results support scientific assumptions that ginseng has got adaptogenic properties in enhancing restoring of complete exercise. It was found that the value of lactate (LT) threshold did not change much [24] during a job to incremental cycle ergometer before and after taking ginseng; were also measured indices of kidney and liver function (aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen and creatinine) [25] to monitor possible side effects of ginseng, they were not subject to increases. Ziemba AW, et al. [26] found in 15 players who took ginseng increased RT (reaction time) but no changes in VO2max during incremental cycle ergometer exercise with increasing intensity of 50 W every 3 min until voluntary exhaustion. Treatment with ginseng shortened RT at rest and during exercise, raising the threshold for mental exhaustion after exercise. Neither ginseng nor placebo affect VO2max and lactacidemia. In conclusion, ginseng extract does not improve aerobic power but improves mental tolerance to exercise.

Recently, [27] the focus has been given to plant-derived saponins for the detection of new adjuvant candidates from traditional Chinese medicinal herbs such as Panax ginseng species of Astragalus, Panax Notoginseng, Cochin momordica, Glycyrrhiza uralensis and Achyranthes bidentata. Many saponins have adjuvant effect on purified protein antigens from the date of its chemical structure and affect the nature of immune responses, stimulates the secretion of a variety of cytokines, acting as a trigger of innate immunity. Therefore have the potential to be used in the design of new vaccines to induce a desired immune response.

Song X et al [28] describes the activity of the immune response up-regulation from ginsenoside-based nanoparticles (ginsomes) in mice. Co-administration of ginsomes with OVA (albumin) significantly increases the levels of specific IgG1, IgG2a, IgG2b and IgG3, as well as was the proliferation of T lymphocytes and B lymphocytes in response to Con A and LPS compared with administration of OVA alone. Parallel with the increase of IgG also increases the production of IFN-γ and IL-5. Therefore, ginsomes are considered as adjuvants in the up-regulation both Th1 than Th2 immune response. Another important finding made by Engels HJ et al. [29] as supplementation with ginseng have not had effects on physiological and psychological parameters such as oxygen consumption (ml / kg per minute), respiratory quotient, ventilation (L / min), blood lactic acid concentration (mmol / L), heart rate (beats / min), and perceived exertion ($P > .05$). Thus there are data that do not consider P ginseng CA Meyer an ergogenic aid to improve performance after submaximal aerobic exercise. Still the same [30] author in another study found no differences between subjects treated with ginseng and placebo non-specific humoral immunity, meaning concentration and salivary flow of sIgA after strenuous physical exercise (Wingate test), nor improves anaerobic power. Miller SC et al. [31] investigated the dose-dependent effects of CVT-E002, an extract of Panax quinquefolius (CV Technologies Inc., Edmonton, AB) in the treatment of a tumor of viral origin, that is erythroleukemia, in mice. The study revealed that the dose of 40 mg / day is particularly effective in stimulating cells of 'non-specific immunity by increasing the lifespan of mice, and reduces the

number of tumor cells in bone marrow and spleen, and significantly stimulates the absolute number and Natural Killer and monocytes. The short-term treatment [32] with ginseng saponin (GS 10 and 20 mg / kg / day) significantly prolonged the aerobic endurance of approximately 70% VO2max altering energy metabolism during prolonged exercise, probably by increasing the use of FFA over glucose for energy metabolism. A further search for active components responsible ergogenic effect of GS, found that a GS preparation devoid of Rg1, and Rb1 had the same ergogenic activities, therefore these two elements were essential to achieve this effect. The purpose of the study of Liang MT et al. [33] was to verify whether a single dose of 1350 mg of Panax Notoginseng (PNG) for 30 days would improve aerobic capacity, strength and mean arterial pressure (MAP) in young adults, it appeared to cause, in fact, better exercise tolerance, and instead reduces MAP and VO2 during exercise resistance. Ginseng is able to change the pattern of certain pro-inflammatory cytokines (TNF-α and IL 1) and gene expression of TRL-4 receptor after stress exercise (swimming) in mice [34]. Min YK et al. [35] studied the red ginseng using it as ergogenic aid for endurance exercise. They studied the expression of 5-hydroxytryptamine (serotonin) synthesis and tryptophan hydroxylase in rat dorsal raphe after taking aqueous extract of red ginseng as a result of exercise on treadmill. In rats to which was administered red ginseng, exercise time increased, and 5-hydroxytryptamine and tryptophan hydroxylase synthase in dorsal raphe were reduced . These results suggest that the suppressive effect of red ginseng at the level of serotonin during exercise is a possible ergogenic mechanism. Voces J, et al. [36] analyzed the enzymatic activity in muscles soleus, gastrocnemius and plantar of mice during exercise and after long term administration of Panax ginseng extract in order to assess the protective role of ginseng against oxidative muscle. The results showed that the enzyme activity of citrate synthase and 3-OH acyl-CoA dehydrogenase had the same changes after exercise with and without ginseng, while the level of lipid peroxidation was effectively reduced by administration of ginseng. The same authors in another study showed [37] Panax ginseng CA Meyer, has been shown to have different biological effects. Treatment with ginseng (100 mg / kg (-1)) protects muscles from injury by eccentric exercise. It was effective in preserving the integrity of the mitochondrial membrane and reduces the nitrate concentration in vastus and rectus (46% and 26%, respectively). It was also detected reduction of carbonyl content of about 27% in all muscles studied. From the same author [38] maintained that Panax ginseng CA Meyer, has protective effect in muscle after eccentric contraction. It has been tested its effectiveness in reducing lipid peroxidation measured by malondialdeide levels, inflammation and release of muscle cell proteins. Although creatine kinase (CK) in plasma was significantly reduced by about 25% after ingestion of ginseng extract, concentrations of beta-glucuronidase and glucose-6-phosphate (G6PDH), considered a marker of inflammation, were significantly reduced.

According to the study of Gaffney BT et al. [39] administration of Eleutherococcus senticosus and Panax ginseng had an ambivalent effect on the testosterone / cortisol ratio, index of stress hormones, meaning that until a certain threshold increased the immune system response to stress, then decreased; other parameters such as lymphocyte subsets and NK remained unchanged. The purpose of Hwang HJ et al. [40] was to analyze the combined effects of regular exercise and ginseng supplementation on peritoneal exudate ROS (reactive oxygen species), lymphocyte proliferation by splenocytes, and DNA damage following exhaustive exercise stress. The results obtained showed that the trained group had a significantly lower mean body weight than the untrained group. With regard to mitogenic activities of splenocytes in response to exhaustive exercise stress, all groups showed much lower lymphocyte proliferative activity when stimulated with media (Med), concanavalin A (ConA), or lipopolysaccharide (LPS) after exhaustive exercise stress. Trained and ginseng-supplemented groups showed lower peritoneal ROS responses and lymphocyte DNA damage levels after exhaustive exercise. The aerobic exercise (swimming) [41] associated with the recruitment of Gin (ginsenosides from stems and leaves of ginseng) regulates lipid metabolism, promotes antioxidant and improves immune activity in mice. In liver tissue were measured total cholesterol (TC), triglycerides (TG), HDL cholesterol (HDL-C) blood, malondialdehyde (MDA) and superoxide dismutase (SOD) and the thymus and liver were weighed. It showed that total cholesterol and triglycerides were reduced significantly, decreased MDA, SOD and HDL-C significantly increased, the thymus weight increased and the liver weight decreased to normal level. Bentler SE et al. explains [42] that even in chronic fatigue syndrome of unknown etiology has been recognized as the use of coenzyme Q10 (69% of 13 subjects), dehydroepiandrosterone (DHEA) (65% of 17 subjects) and ginseng (56% of 18 subjects) had stimulating effects on physical performances.

Smith AE, et al. [43] conducted a study comparing a group taking placebo with a group taking during training a mixture consisting of 18 grammes Ginseng, Creatine, Citrulline, Cordiceps Sinensis and caffeine were monitored and the VO2max (cardiovascular fitness with open circuit spirometry), the CV (critical velocity), ARC (aerobic capacity), LBM (lean body mass) and were improved compared to placebo.The results of this study Allen JD et al. [44] do not support an ergogenic effect

of Panax ginseng. Assumption of ergogenic supplements [45] containing Eleutherococcus senticosus (ES), a plant also known as ciwujia or Siberian ginseng is very common among athletes. Eleutherococcus senticosus improves cardiorespiratory fitness (CF) and fat metabolism (FAM) and as a consequence, endurance performance (EP). During physical endurance exercise, ES greatly improves CF, FAM and EP. On the other side, 5 studies do not show any advantage of ES on CF, FAM and EP. It is therefore assumed that ES (1000 to 1200 mg / die per 1-6 weeks) has no ergogenic activity.

In a study from Hwan Kim S, Jun Lee W, Byrne HK [46] the effect of ginseng as anabolic steroid after physical exercise was evaluated and no effective alterations of growth hormone, testosterone, cortisol and insulin-like growth factor 1 (IGF-1) after ginseng assumption were found together with no significant alterations of the previous ones.

By studying Biondo PD et al. [47] it was found that administration of ginseng reduces the concentration of CD8 + T cells in peripheral blood and increases the production of stimulating factors (IL-2) release of T cells. Taking ginseng had no effect on blood total leucocyte count, concentrations of neutrophils, monocytes or lymphocytes (CD3 +, CD4 +, CD16 +, CD20 +), lymphocyte proliferation, or oxidative burst in neutrophils. Ginseng did not significantly affect the changes induced by exercise, plasma concentrations of lactate, insulin, cortisol and growth hormone. The consumption of ginseng for 5 weeks then had a limited effect on the immune response. Other authors regarding [48] the effectiveness of ginseng on the improvement of physical performance has not been demonstrated for the lack of scientific studies and [49] and for non-response of significant ergogenic effects from the administration of ginseng.

CONCLUSIONS

In consideration of the clinical data collected in the international literature, we can conclude that the administration of these herbal supplements (Echinacea Purpurea, Rhodiola Rosea, Panax Ginseng) generally do not present significant ergogenic effects nor anabolizing effects, but they have shown adaptogenic properties, based on biological effects on the immune system.

In the case of Echinacea the effect on the immune system is stimulating on all cytokins as to the root, while the leaf has an immuno suppressive action, so the root extract can be indicated for prevention of the infections of the upper airways, which are common in exhaustive endurance sports (marathon).

As to Rhodiola Rosea, its extract contains substances which are able to modulate the neurotransmission involved in the central fatigue, therefore it allows a slight bettering of the psychophysical performance, as a greater resistance to stress from aerobic exercise, but it overall makes to recover more rapidly from oxidative membrane damage and stimulates all the cell lines of the immune system, with adaptogenic effects like Echinacea.

Panax Ginseng isolated does not have in most of studies significant effects on the energetic metabolism nor on aerobic and anaerobic power of the athlete, but it is surely able to decrease greatly the lipid peroxidation and consequently the membrane damage from eccentric exercise in the muscular fibres : it is important in the prevention of the overuse diseases and in accelerating the recover times.

None of the three supplements has determined adverse reactions in the studies we examined, so their use in endurance sports with mainly adaptogenic aims can be recommended.

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