©Journal of Sports Science and Medicine (2011) **10,** 315-321
http://www.jssm.org

Research article

Effect of *phlebodium decumanum* on the immune response induced by training in sedentary university students

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Abstract
Exercise training is considered a good model to provoke different degrees of immune dysfunction affecting physical performance and some physiological responses related to oxidative stress and low grade inflammation. *Phlebodium decumanum* is a polypodiaceae may induce shown immunomodulating effects, specifically directed to the release of proinflammatory cytokines by macrophages in response to various stimuli, as reported different in vitro studies. The aim of this study was to evaluate the modulating effect of *phlebodium decumanum*, on the immune response induced by physical exercise. Thirty-one subjects (males only) were randomly divided into two groups: Group PD (n = 18); age: 22.1 ± 1.81, weight 74.21 ± 8.74 kg) that was treated with *phlebodium decumanum*; Group P (n = 13); age: 22.5 ± 1.63, weight 78 ± 12.5 kg) that was treated with a placebo. Before and after one month training program performed by both groups (three times a week), the following performance parameters and immune response variables were measured: Dynamic Maximum Force; Interval-Training; Tennis test; pro-inflammatory (TNFα, IL6) and anti-inflammatory (TNF-IIrs, IL1-ra) cytokines levels. Data were statistically analyzed with Mann-Whitney U test and Wilcoxon paired test ($p < 0.05$). Statistically significant differences were recorded within groups before and after the training program. PD group showed a significant improvement in the performance parameters (Strength Muscle Test: dorsal: $p < 0.002$; deltoids: $p < 0.03$; and pectorals: $p < 0.07$; Interval Training: $p < 0.06$; Tennis Test: $p < 0.02$). Cytokine levels resulted in a more positive profile in the PD group rather than in the P group, in which higher levels of IL-6 ($p < 0.02$) and a reduction of TNF-IIrs ($p < 0.003$) and IL1-ra ($p < 0.03$) were recorded. In this study the use of *phlebodium decumanum* demonstrated beneficial effects in the modulation of the immune response during physical performance.

Key words: Physical exercise, inmunomodulation, TNFα, IL6, TNF-IIrs, IL1-ra.

Introduction

Immune system is a complex network in which different kind of cells and molecules work together to protect our body. Its function is directed to specifically recognizing molecules or antigens for developing an effective response against inflammation or infection attacks. Immune system activity represents an essential defense against infections and cancer. Successful response depends on specific cells activation (lymphocytes and accessory cells) and antibodies production. Nevertheless, an inadequate reaction may induce negative effects in the host, determining inflammation and tissue damage (Ciliberti et al., 2009).

Immune system cells function is regulated by the action of specific molecules called cytokines, mainly lymphokines and monokines. Cytokines are secreted by lymphocytes and monocites to control the proliferation and differentiation of immune system cells (Sigal and Ron, 1994), and from the structural point of view, they are soluble low molecular weight proteins, peptides and/or glycoproteins that participate and mediate the control and communication between cells involved in the immune response. There are almost fifty different types of cytokines that have been classified according with their physiological activity: pro-inflammatory, antiviral, immune-stimulating, hematopoyetic, anti-inflammatory or immunoregulating activity (Nieman, 1997).

Inflammation is one the most evident effects provoked when performing physical exercise. Its extent depends on the variables describing exercise like, duration, intensity, frequency, etc. (Ploeger et al., 2009). Many studies reported that performing moderate physical exercise might be beneficial for stimulating immune system efficiency (Klentrou et al., 2002). On the contrary, stress generated by intense or long duration training may deteriorate its function (Córdova et al., 2010), provoking an immune dysfunction effect.

The understanding of immune system alterations, resulting from prolonged physical exercise, is the first step to design preventive or therapeutic strategies against functional problems associated with sports activities. Immune system modulation results in beneficial effects in sport performance (Cordova and Alvarez-Mon, 1999a; 1999b).

Currently, there are some drugs and nutritional complements, like acetyl salicylic acid (Aspirin®) or glicofosfopeptical (Inmunoferon®), that show an immunomodulatory activity. The latter one, has shown a strong anti-inflammatory effect, resulting in pro-inflammatory cytokines inhibition (i.e.TNFα). Moreover, it may reduce proteins serum levels associated with muscle damage (Villarrubia et al., 1997). Similarly, Ibuprofen® has been used as immunomodulator therapy for preventing muscle damage during intense physical exercise (Hasson et al., 1993).

Phlebodium decumanum is a Polypodiaceae grow-

Received: 06 January 2011 / Accepted: 22 February 2011 / Published (online): 01 June 2011

ing in some specific areas of Central America. The variety used in this study was grown in the pure, organically processed monoculture located in the vicinity of the Yojoa Lake (Northern Honduras). Different compositions comprising a purified and standardized water-soluble fraction obtained from the leaves of *phlebodium decumanum* (EXPLY) have shown their immunomodulating effect, specifically directed to the release of TNF by macrophages in response to various stimuli. They seem to have a buffer action on the levels of TNF, playing a role in the regulation of the homeostasis of pro-inflamatory cytokines (Punzon et al 2003). Both nutritional supplement (functional food) and energetic drink status have been granted to different compositions containing EXPLY. Moreover, different patent applications on the use of *phlebodium decumanum* in the correction of the overtraining syndrome have been filed (P-9900133®).

The immunomodulation activity of *Phlebodium Decumanum* has been evaluated in different *in vitro* (Gridling et al., 2009; Punzón et al., 2003) as well as *in vivo* investigations (Tuominen et al., 1991, Vasänge et al., 1994; 1997).

The aim of this study was to evaluate the modulating effect of *phlebodium decumanum* on immune responses resulting from intense physical exercise, and its hypothetical benefits on physical performance in sedentary adults.

The specific purposes of this study were the assessment of:

1. The adaptative changes in basal immunological parameters in response to aerobic training.
2. The effects of Phlebodium decumanum both on said changes and on those induced by high intensity, anaerobic exercise.

Four types of cytokines have been evaluated in this study. Two of them are usually considered as pro-inflammatory cytokines: Tumour Necrosis Factor (TNFα) and Interleukin-6 (IL-6). On the other hand, IL-1 receptor antagonist (IL-1ra) and soluble tumour necrosis factor receptor 2 (sTNFR2) as anti-inflammatory molecules.

Methods

Fifty students belonging to the Cardenal Spinola (University of Seville, Spain) were selected for the study. All individuals gave written informed consent to be included in the study, which was performed in accordance with the guidelines proposed in the Declaration of Helsinki. Students were randomly divided into two groups: Experimental (25 GPD) and Placebo (25 GP) in order to perform a double-blind multigroup trial.

Subjects were equally distributed in the two groups according to their maximum oxygen consumption (VO_{2max}) that was measured with a protocol based on maximal treadmill graded exercise test (Runrace D-140, Technogym, Italy) and a gas analyzer (Oxicon Delta, Jaeger, Germany): the latter is based on an infrared and a paramagnetic system that were used for measuring CO_2 and O_2 levels, respectively. According to the results achieved in the test, subjects were distributed in the two groups (n = 25), although the study was finally carried out with 31 subjects distributes as follows: 18 subjects in the GPD group (mean age: 22.1 years (1.81); mean weight: 74.21 (8.74)); 13 subjects in the GP group (mean age: 22.5 years (1.63); mean weight: 78.0 (12.5)).

All the subjects included in the study were used to play tennis sporadically and did not participate in any other investigation. None of them belonged to an official tennis federation nor participated in any official competition.

400 mgr capsules containing 250 mgr of frond hidrosoluble extract and 150 mgr of polverized rhizome of *phlebodium decumanum* (patent no. P-9900133) were given to the subjects belonging to the Experimental group (2 capsules-3 times/day). Subject belonging to the Placebo group were treated with 400 mgr capsules containing brewer's yeast (2 capsules - 3 times/day). The nutritional supplements were distributed by the Helsint S.A.L. (Madrid, Spain) and the treatment was performed during 4 weeks.

Nor the subjects neither the operator knew which type of medicament was taking during the test. All subjects were also included in a training protocol during 4 weeks (3 times/week). Each session was divided into three parts:

1º: Tennis strokes in a tennis court. Working in pairs, each subject executed 500 strokes as follows:

125 parallel forehand; 125 cross forehand; 125 parallel backhand and 125 cross backhand strokes.

2º: Dynamic force training. It consisted on training three muscles groups:

- Pectoral muscles: Bench press;
- Dorsal muscles: Lat pull-down behind neck;
- Deltoids muscles: shoulder dumdbell press.

Each series was performed with an intensity of 55%-60% (between 15 and 20 maximum repetitions) (Brzycki, 1993). Three series of each exercise were performed during the first two weeks increasing up to four series during the last two weeks of training with a recovery time of 2 minutes.

3º: Resistance training. It was performed through an interval training protocol performing a round way race over an eight meters distance at maximum intensity, thus running a total of 160 meters.

The recovery was decided according to the heart frequency measured with a heart rate monitor (Polar® Vantage NV, Polar Electro OY, Finland) when it reached a value of 125-130 bpm. This training program had a duration of 20 minutes during the first two weeks, 25 minutes during the third and forth weeks and 30 minutes during the first and last sessions.

Blood levels of Tumor Necrosis Factor Alpha (TNFα), Interleukin-6 (IL-6), Interleukin-1receptor antagonist (IL-1ra) and Soluble TNF II receptor (TNF-IIrs) have been measured before and after completing the training program together with the physical performance using specific tests.

Blood samples were collected in glass tubes containing 35 micromol dipotassium-EDTA that were

Table 1. Descriptive statistics of performance parameters recorded in the tested groups.

	PLACEBO GROUP			*PHLEBODIUM DECUMANUM* GROUP		
	Mean	**N**	**SD**	**Mean**	**N**	**S.D.**
Pectorals-pre-test	43.88	13	14.41	39.58	15	11.42
Pectorals-post-test	45.11	13	12.47	47.02	15	10.08
Pectorals (%)	**4.94**	**13**	**17.06**	**24.31**	**15**	**25.83**
Dorsal-pre-test	48.54	13	13.03	47.11	16	13.57
Dorsal-post-test	51.82	13	13.37	56.43	16	14.36
Dorsal (%)	**7.59**	**13**	**9.52**	**22.35**	**16**	**19.11**
Deltoids-pre-test	21.06	13	4.65	18.87	18	6.54
Deltoids-post-test	24.58	13	9.03	26.80	18	7.20
Deltoids (%)	**16.30**	**13**	**29.82**	**50.82**	**18**	**40.06**
Interval-training pre-test	7.69	13	2.36	7.83	18	2.07
Interval-training post-test	9.62	13	2.10	11.83	18	1.86
Interval (%)	**30.29**	**13**	**28.3**	**59.04**	**18**	**42.01**
Tennis pre-test	72.17	12	39.23	59.24	17	27.51
Tennis post-test	109.67	12	55.15	112.35	17	45.37
Tennis (%)	**58.09**	**12**	**33.13**	**101.47**	**17**	**54.88**

centrifuged during 30 minutes (3758 rpm) at 4º C. The blood serum obtained was separated in two Eppendorf tubes labeled with a personal code and stored at -80ºC.

The analysis was performed using an enzyme-linked immunosorbent assay (ELISA; R&D systems, Minneapolis, MN, USA)

Tennis physical and technical performances were also evaluated in a tennis court through a tennis ball machine (KALENDA®, SPAIN) according to the procedure previously described by Van Dam and Pruimboom (Dam and Pruimboom, 1992).

Maximal dynamic force has been also evaluated through a sub-maximal test and according to a mathematical formula previously described by Brzycki (1993) that expresses this value starting from the sub-maximal weight value (i.e. 10 RM or 12 RM).

The number of repetitions realized by the subjects during the first and the last training days has been also taken into account.

The same operator controlled all the subjects included in the study as well as the training sessions that were performed daily under the same conditions with no differences between groups.

Statistical analysis

Values recorded for each variable before and after completing the study were checked for normal distribution (Shapiro-Wilk) comparing them within the group and between groups. Normally distributed data were analyzed with t-Student test ($p< 0.05$). No normally distributed data were analyzed using Mann-Whitney U test and Wilcoxon test ($p<0.05$). The statistical analysis was handled with SPSS 11.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Mean (SD) values of the variables evaluated in the study have been summarized in Tables 1 and 2.

Table 2. Descriptive statistics of cytokines levels recorded in the tested groups (pg/ml).

	PLACEBO GROUP			*PHLEBODIUM DECUMANUM* GROUP		
	Mean	**N**	**SD**	**Mean**	**N**	**S.D.**
IL-6 pre-test	2.90383	13	2.88930	3.43582	18	3.32601
IL-6 post-test	3.52158	13	3.44677	2.32118	18	2.37864
IL-6 (%)	**64.59250**	13	**134.54459**	**-17.88824**	18	**68.43066**
TNF pre-test	11.85000	13	15.58920	16.28305	18	24.50650
TNF post-test	1.64877	13	3.86255	7.51721	18	14.15368
TNF (%)	**-47.78154**	13	**56.64041**	**-20.54111**	18	**106.28531**
IL1-ra pre-test	214.45009	13	65.42412	153.33815	18	72.41709
IL1-ra post-test	194.50643	13	49.23782	189.83245	18	102.49012
IL1-ra (%)	**-5.62538**	13	**20.41236**	**29.61529**	18	**47.80039**
sTNF-RII pre-test	.31623	13	.24350	.19694	18	.10147
sTNF-RII post-test	.26723	13	.22726	.21012	18	.11515
sTNF-RII (%)	**-18.59462**	13	**24.74515**	**6.94706**	18	**18.15820**
Tennis pre-test	72.17	12	39.23	59.24	17	27.51
Tennis post-test	109.67	12	55.15	112.35	17	45.37
Tennis (%)	**58.09**	**12**	**33.13**	**101.47**	**17**	**54.88**

Interleukin-6 (IL-6), Tumor necrosis factor (TNF), Interleukin-1 receptor antagonist (IL1-ra), Soluble TNF receptor II (sTNF-RII)

Pro-inflammatory cytokines levels

Pretest and post-test mean IL-6 values recorded in the tested groups have been summarized in Figure 1. A significant reduction in the plasma levels of IL-6 was observed in the PD group ($p < 0.039$). On the contrary, a slight improvement in the IL-6 plasma levels has been recorded in the placebo Group, although it was not significant ($p = 0.53$).

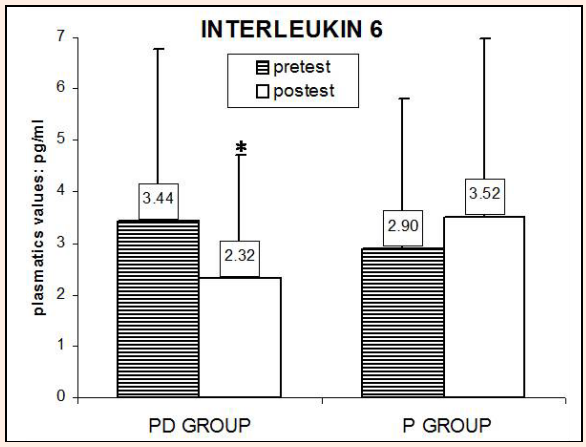

Figure 1. Pretest and post-test mean IL-6 values recorded in the tested groups. * $p < 0.05$.

Pretest and post-test mean TNF-α values recorded in the tested groups have been summarized in Figure 2. A reduction in the plasma levels was observed in the PD ($p < 0.05$) and P group ($p < 0.06$) after performing physical exercise.

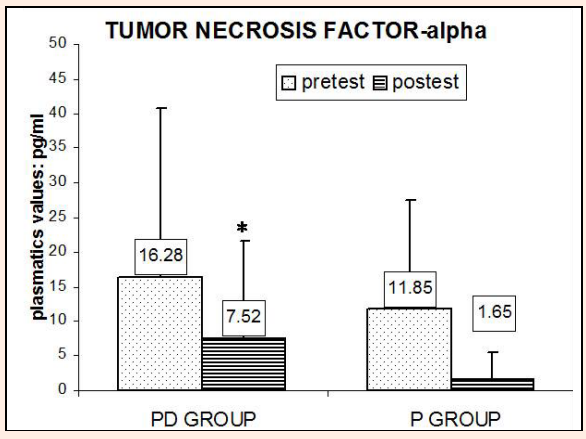

Figure 2. Pretest and post-test mean TNF-α values recorded in the tested groups. * $p < 0.05$.

Anti-inflammatory cytokines levels

A comparison between the IL-1 plasma levels within the experimental groups has been reported in Figure 3. IL-1 levels improved significantly in the PD Group ($p < 0.026$), while a reduction occurred in the P Group, although not statistically significant ($p = 0.146$).

A comparison between the TNF-IIrs plasma levels within the experimental groups has been summarized in Figure 4. TNF-IIrs plasma levels improved significantly in the PD group ($p < 0.04$), while the P Group attained a statistically significant reduction ($p < 0.036$).

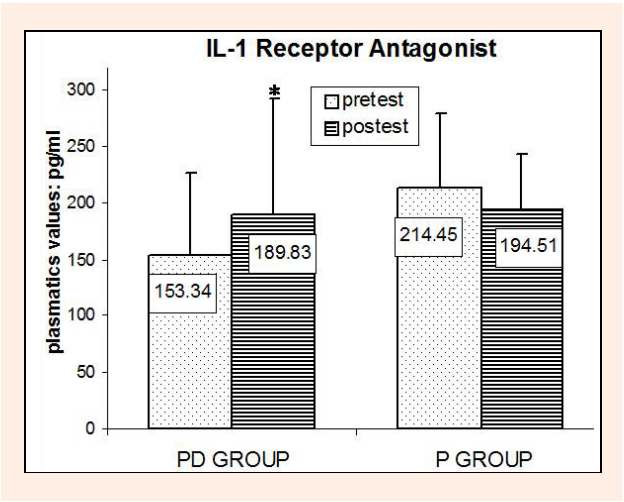

Figure 3. Comparison between IL-1 plasma levels recored within the experimental groups. * $p < 0.05$.

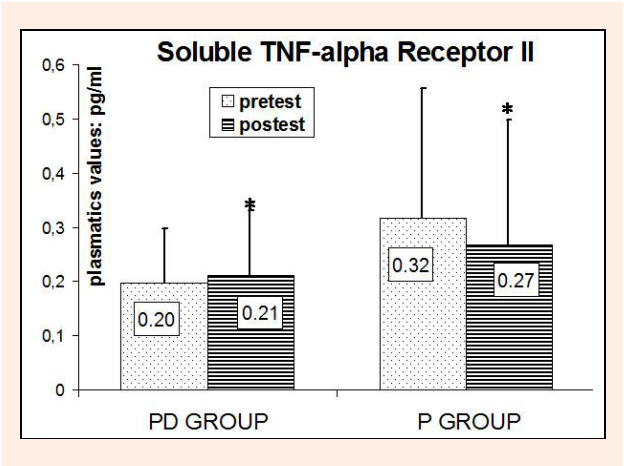

Figure 4. Comparison between the TNF-IIrs plasma levels recorded within the experimental groups. * $p < 0.05$.

Moreover, an evaluation of the starting values of the tested variables was performed in the study, to assess the homogeneity between the two experimental groups. No significant differences have been recorded for IL-6, TNF-alpha, y TNR-IIrs (Mann Whitney U test: $p = 0.38$, $p = 0.6$ y $p = 0.3$, respectively). Higher levels of IL-1ra have been detected in the pre-test P group ($p < 0.025$). Change levels expressed in percentage have been compared in order to evaluate the existence of differences between the experimental groups recorded after training. Changes in cytokine levels between pre-test and post-test experimental Groups (expressed as percentages) have been summarized in Figure 5. Significant differences within groups have been recorded for all the cytokine evaluated in the study, except for TNFα. This evaluation was performed using Mann Whitney U test for IL-6 ($p < 0.02$), IL1-ra ($p < 0.03$) and TNFrsII ($p < 0.003$) while t Student test was applied for TNFα ($p = 0.36$).

Discussion

Changes in cytokines levels during the inflammatory

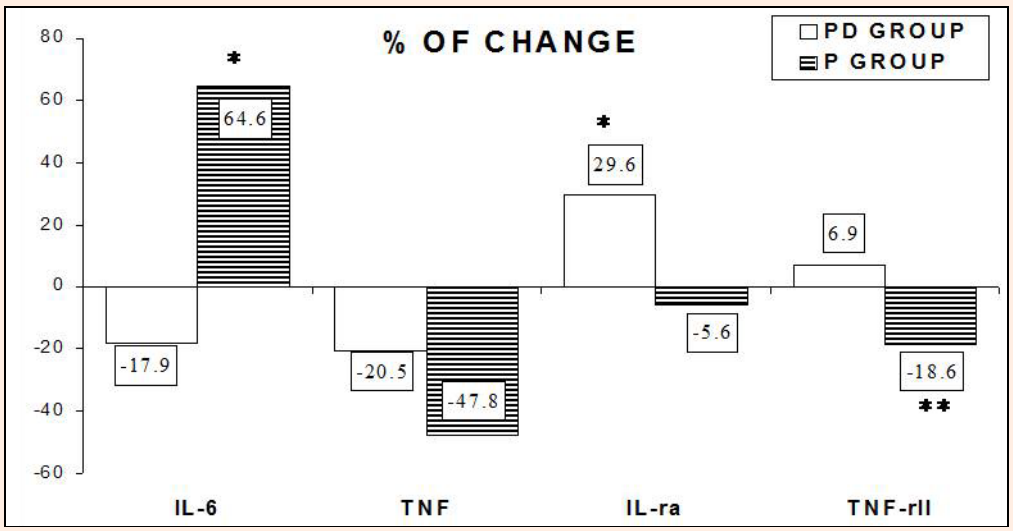

Figure 5. Percentages of changes in cytokine levels recorded between pre-test and post-test experimental groups. * $p < 0.05$, ** $p < 0.01$.

response induced by intense physical exercise differ from that observed during infection (Ostrowski et al., 1999; Pedersen and Toft, 2000; Petersen and Pedersen, 2005; Suzuki et al., 2002).

In the latter, cytokines plasma levels are used to be as follows: TNFα, IL-1, IL-6, IL1ra, sTNF-IIR (Agha Alinejad and Molanouri Shamsi, 2010; Moldoveanu et al., 2001; Pedersen and Toft, 2000).

During physical training IL-6 plasma levels considerably improve with a subsequent reduction in the post-training period (Pedersen et al., 2003; 2004).

Higher TNFα and IL-6 levels have been recorded immediately after completing the training program, while IL1ra and sTNF-IIR higher percentages were accomplished after one-hour recovery (Ostrowski et al., 1999; 2001; Petersen and Pedersen, 2005; 2006, Ruth et al., 1996; Tilg et al., 1997).

IL-6 is considered the main mediator of the acute response and it is activated in case of stressing situations, like physical training. IL-6 regulates TNFα levels, through a mechanism that lowers its production. So TNFα plasma levels may not improve during training and even diminish, as reported by previous investigations (Agha Alinejad and Molanouri Shamsi, 2010; Croft et al., 2009; Gray et al., 2008; Moldoveanu et al., 2001; Nielsen and Pedersen, 2007; Pedersen et al., 2004; Petersen and Pedersen, 2006; Steensberg, 2003; Suzuki et al., 2002)

The results of this study showed that IL-6 plasma levels improved 48 hours after training in the Placebo group, although not significantly. Many studies reported that the improvement of this cytokine depends on the magnitude of the physical effort. Although the improvement of IL-6 is evident, these levels are temporary and tend to lower after finalizing the physical training. (Bruunsgaard et al., 1997; Croft et al., 2009; Drenth et al., 1995; Gray et al., 2008; Moldoveanu et al., 2000; Ostrowski et al., 1998; Pedersen et al., 2004; Petersen and Pedersen, 2006). However, in this study the measurements were performed 48 hours after finalizing the last training session. On the contrary, IL-6 plasma levels significantly lowered in the PD Groups ($p < 0.05$). Significant differences existed in the percentage of IL-6 levels between the two groups before and after the training program ($p < 0.02$).

Previous investigations reported that TNFα plasma levels improve after an extreme endurance training (Drenth et al., 1995; Moldoveanu et al., 2000; Ostrowski et al., 1999). Comparing pre- and post-training data, this study highlighted a significant reduction of these levels in both groups ($p < 0.05$) with no significant differences between them ($p = 0.35$). Discrepancies may be due to the fact that in this study the analysis were preformed 48 hours after completing the last training session, while in other studies the improvement is registered immediately after completing the training session or after few hours.

The results are in agreement with previous investigations that reported a significant reduction or even no changes in TNFα levels after physical training (Gokhale et al., 2007; Suzuki et al., 2002). According to Moldoveanu et al. (2000; 2001) TNFα regulation induced by physical exercise depends on the intensity and on the duration of the physical stimulus.

Once the latter phase was completed, high TNFα plasma levels were maintained only for a short period of time, thus making difficult its accurate measurement after physical training. Anti-inflammatory cytokines IL-1ra and TNF-IIrs had a similar behavior. IL-1ra inhibits the activity of IL-1, lowering its potential adverse effects (Cordova and Alvarez-Mon, 1999b; Cordova and Alvarez-Mon, 1999a; Ruth et al., 1996).

Several studies reported an improvement of anti-inflammatory cytokines, like IL-1ra, due to physical training (Nieman, 1997; Nieman et al., 2006; Suzuki et al., 2000). Although physical training determines an improvement in pro-inflammatory cytokine levels, this response is balanced thanks to the production of cytokines with an inhibitory effect over the inflammatory ones (IL-1ra and TNF-IIrs) (Ostrowski et al., 1999). It may be speculated that anti-inflammatory cytokines reduce the amount and duration of the inflammatory response due to

physical exercise.

In this study, both IL-1ra and TNF-IIrs plasma levels were reduced in the GP group after training. This reduction was statistically significant only for TNF-IIrs ($p < 0.05$), while no significant differences have been recorded between IL-1ra pre- and post-training levels ($p = 0.14$). In the PD Group plasma levels of both IL-1ra and TNF-IIrs improved significantly after training ($p < 0.05$). The statistical analysis revealed significant differences between the two tested groups for both the tested parameters (IL-1ra: $p < 0.03$ and TNF-IIrs: $p < 0.003$, respectively). These results are in agreement with previous investigations that highlighted the influence exerted by IL-6 on IL-1ra, IL-10 (Emmanuel and Lie, 1996; Ronsen et al., 2002; Ruth et al., 1996; Steensberg, 2003) and TNF-IIrs production (Cordova Martinez et al., 2006; Drenth et al., 1998; Tilg et al., 1997).

Conclusion

The results of this study show that immune response indicators levels may be affected by practicing sport or physical activity of medium-high intensity. *Phlebodium decumanum* demonstrated a beneficial effect in this study, inducing a reduction in pro-inflammatory cytokines levels and a higher concentration of anti-inflammatory cytokines. Their protective and modulating effect on the immune response has been highlighted.

Acknowledgements

We are grateful to the Helsint S.A.L. for its financial support for this study.

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Key points

- Practicing sport or physical activity of medium-high intensity three times a week during 4 weeks induces changes in immune response indicators levels;
- The assumption of *phlebodium decumanum* induced a reduction in pro-inflammatory cytokines levels and a higher concentration of anti-inflammatory cytokines.
- Anti-inflammatory cytokines have a protective and modulating effect on the immune response.

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