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Original Research

Supplementation with SEPIFIT™ Protect, a complex of a natural red wine extract, vitamin E and zinc, improves exercise recovery in healthy men

Abstract

A period of intense or prolonged muscle activity can cause a decline in performance, which can range from muscle weakness to muscle damage and soreness. Muscle fatigue can be largely reversible in minutes or hours. It is generally viewed to be the result of insufficient energy and a lack of availability of key metabolites that enable contracting muscles to meet increased energy demand. However, muscle recovery can fail to take effect quickly, and this can be associated with structural changes and damage within the muscle, inducing a cascade of events leading to immediate or delayed soreness. In previous research, SEPIFIT™ Protect, a combination of natural red wine polyphenols, zinc and vitamin E, showed in *vitro* efficacy with respect to lactate, interleukin-6 and creatine kinase, which are markers of muscle damage and fatigue.

We have therefore conducted a pilot clinical study to evaluate the effects of this active complex in healthy men undertaking regular and stable physical activity and who were subjected to a pain induction protocol. The results showed that the consumption of 135 mg of the complex per day for 12 days was effective in reducing creatine kinase release and maintaining muscular power capacity after the pain induction protocol.

It also induced a better perception of performance, physical condition and muscle soreness. SEPIFIT™ Protect can thus be considered an interesting complex to contribute to muscle recovery during physical exertion.

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Introduction

Periods of intense or prolonged muscle activity can cause a decline in performance, which can be measured as muscle weakness. Muscle fatigue can be largely reversible in minutes or hours, or muscle recovery can fail to take effect quickly and this can be associated with structural damage within the muscle. Even though it is usual to make a distinction between muscle fatigue and muscle damage, the two phenomena undoubtedly overlap.

Muscle fatigue is generally viewed to be the result of insufficient energy and a lack of availability of key metabolites that enable contracting muscles to meet increased energy demand. After prolonged physical activity, muscles become fatigued and can no longer contract, even when signalled by the nervous system to do so [1]. Multiple mechanisms can explain muscle fatigue; for example, acidosis and depletion of ATP. Muscle acidosis is thought to interfere with muscle contraction mechanisms. It also reflects the fact that the generation of aerobic ATP is insufficient and needs to be supplemented with anaerobic ATP generation, leading to a more rapid consumption of glycogen in muscle cells [2] and to the production of lactate, which can then be considered a marker of muscle fatigue [3]. Physical exercise also induces interleukin-6 (IL-6) production and release by contracting muscle cells. Plasma IL-6 levels increase dramatically (up to 100-fold) in response to exercise, and its production is associated with contracting muscles. During physical exercise, IL-6 is regularly detected in plasma [4] and it is thought to act like an energy sensor to maintain glycaemic homeostasis [3,4]. Furthermore, IL-6 contributes to sensations of fatigue during exercise and can also be considered a marker of muscle fatigue [5,6].

Muscle damage is characterized by structural abnormalities, including sarcomeric disorders and membrane damage, resulting in the release of cellular components, an increase in muscle protein degradation and cell permeability, and also, inflammatory processes [1,2]. This phenomenon is defined as exercise-induced muscle damage (EIMD). Unaccustomed or strenuous exercise can initiate EIMD of varying degrees. Damage is particularly pronounced in muscles that are stretched during contractions. Muscle damage induces a cascade of events leading to immediate soreness or delayed-onset muscle soreness (DOMS) [7]. Muscle soreness refers to the immediate soreness perceived by the athlete while or immediately after participating in exercise, in combination with muscle stiffness, aching pain and/or muscular tenderness. These symptoms are experienced only for hours and are relatively transient. The symptoms associated with DOMS are the same as for immediate soreness but the onset of symptoms occurs approximately 24 hours after the athletes have completed their exercise. The symptoms continue for 72 hours and slowly resolve in five to seven days [8]. DOMS is perhaps one of the most common and recurrent forms of sport injury [9]. Loss of myofibre proteins into the blood may occur at several stages along the continuum of muscle injury to muscle soreness. Creatine kinase (CK) is one of the proteins that are leaked into the circulation when muscle damage occurs. Moreover, as CK is almost exclusively present in muscular tissue, it is currently analyzed in serum to evaluate muscle damage and injury [1].

SEPIFIT ™ Protect (SPro) is a patented active complex containing a natural red wine extract, vitamin E and zinc. The effects of this active complex have already been investigated in an in *vitro* model, which mimicked strenuous physical exercise in muscles by stimulating human skeletal myofibres with a calcium ionophore (inducing muscle contractions). This stress brought about an increase in lactate and IL-6 release, and a decrease in intracellular CK

activity. The SPro complex was able to reduce the release of lactate and IL-6 and preserve intracellular CK activity. These results indicated that SPro was a good candidate to protect muscles from fatigue and damage induced by strenuous physical exercise [10].

The objective of the present clinical study was to evaluate the effects of SPro on muscular recovery management, with healthy men subjected to a physical exercise pain induction protocol. The efficacy of SPro was determined by assessing the release of muscle fatigue and damage markers, completed by a functional test.

Materials and methods

Materials

The active product being tested, SPro, is a patented active complex containing a natural red wine extract, vitamin E and zinc. The natural red wine extract was chosen for its more than 200 phenolic compounds, which are specific and distinct from those found in grape extracts, coming as they do from the wine manufacturing process (maceration, fermentation), with an additional step to remove the alcohol content. It also has an extremely high antioxidant capacity. The natural red wine extract content in SPro matches the intake of polyphenolic compounds from one glass of red wine, the daily consumption of which has been shown to have health benefits in epidemiological studies [11]. This ingredient brought about a greater improvement in blood pressure than the equivalent polyphenol-rich grape extract versus placebo in mildly hypertensive subjects, showing its clinical potential [12]. Vitamin E refers to a group of compounds that includes both tocopherols and tocotrienols. α-Tocopherol, the most biologically active form of vitamin E, is the second-most common form of the vitamin in the diet (after γ-tocopherol). Vitamin E has many biological functions, including a role as a fat-soluble antioxidant. Zinc is an essential mineral, recognized today as being important for health. Both vitamin E and zinc are well recognized for their roles in protecting cells from oxidative stress, and both support an authorized health claim in the European Union (Regulation (EC) No 1924/2006). The dosages of vitamin E and zinc in SPro at the recommended daily dose allow the use of vitamin E and zinc authorized claims for SPro.

The recommended daily dose of SPro is 135 mg per day. The test products were in the form of a dietary supplement formula in a capsule shape (total weight: 445 mg) containing maltodextrin (435 mg for the placebo group and 300 mg for the SPro group), magnesium stearate (10 mg) and SPro (135 mg for the active group). Volunteers consumed 1 capsule daily in the morning for 12 days.

Participants

Male participants, aged between 18 and 40 years old, undertaking regular and stable physical activity of between 1.5 and 4.5 hours per week for at least 3 months, were included in the study. Participants were non-smokers or individuals with a tobacco consumption of fewer than 10 cigarettes per day. Exclusion criteria were the use of treatment and/or dietary supplements and/or 'health foods', which could significantly affect measured parameters. Subjects were also asked not to change their dietary habits. All participants gave written informed consent before participation. The study was approved by the ethical committee and conducted in full accordance with the principles of the 1975 Declaration of Helsinki, revised in 2000. The study was performed in France by an independent contract research organization.

Design and protocol

The study was designed as a pilot randomized, parallel-group, double-blind trial

to test the effects of a daily dose of 135 mg of SPro versus a placebo over a period of 12 days.

Inclusion visit V1

The study started with an inclusion visit (V1) to check inclusion criteria, particularly physical activity habits, to randomize subjects and to give them test products. During this visit, subjects completed the IPAQ-SF (International Physical Activity Questionnaire-Short Form) and were included if the volume of their intense physical activity was between 1.5 and 4.5 hours per week. The IPAQ-SF was used for the estimation of physical activity. The total metabolic equivalent was calculated from the questionnaire. This score, expressed as MET-min per week (with MET = the estimated metabolic equivalent of task), was calculated using the following formula:

$$\text{Total MET-min/week} = \sum_{\text{activities}} \text{MET} \times \text{min} \times \text{days}$$

where MET represents the amount of energy expended during physical activity: walking = 3.3 MET, moderate physical activity = 4 MET and vigorous physical activity = 8 MET.

The subjects then received test products, either active or placebo, according to the randomization list, for 12 days of consumption until the next visit. 12 days later, the subjects returned for visit V2, to evaluate parameters before and after the pain protocol induction.

Pre-induction visit V2

As requested at visit V1, subjects had to complete the IPAQ-SF again, to confirm that they had not changed their physical activity. They also completed a questionnaire on product satisfaction and, more specifically, on the product's efficacy with respect to their performance in their usual sport (modalities from 'insufficient' to 'sufficient', 'quite good' and 'excellent'), physical condition and muscle soreness (modalities from 'not at all' or 'mostly not' to 'mostly yes' and 'yes, totally').

A capillary blood sample was then taken from the finger for analysis of CK and lactate. Muscular power capacity was evaluated by a functional capacity test that consisted of a concentric contraction test (squat jump): the subjects had their knees bent with a fixed angle as the start position. They then had to jump as high as possible, and vertical elasticity was assessed (jump height in cm). Three sessions were performed and the best attempt was taken as the result. In parallel, during the test, power was measured with an accelerometer placed on the subjects' hips (expressed in watt/kg).

Pain induction protocol

The pain induction protocol was necessary to mimic physical exertion and to induce muscular pain in the subjects in order to observe the effects of the study product on muscular recovery. This protocol (adapted from [13]) consisted of 2 different exercises:

- Series of little hurdle jumps (40 cm): the subjects had to jump these hurdles with a precise bending angle. They had to perform 5 series of 10 jumps each (30 sec of rest between series);
- Series of down-below jumps (drop jump), after 2 min of rest: the subjects were standing on an elevated platform (50 cm high) and had to jump down with a 90°angle (with straight head and back). They had to perform 5 series of 10 repetitions each (30 sec of rest between series).

Post-induction visit V2

After pain induction, another capillary blood sample was taken from the finger, for analysis of CK and lactate levels. Muscular power capacity was also evaluated using the functional capacity test.

Statistical analysis

As this was a pilot clinical study on SPro, no calculation of the number of subjects was

possible. It was therefore decided to include 15 subjects per group, after an analysis of published guidelines on an appropriate sample size for a pilot study (recommendations varied from 10 to 40 subjects). Analysis was performed on the ITT (intention-to-treat) population. Missing data were not replaced. For each parameter and each group, the mean and standard deviation were calculated. Variations (deltas) were also calculated, according to the following formula: Delta (parameter) = Value (V2 post-induction) - Value (V2 pre-induction). Comparison between the products was based on delta values, using one-way ANOVA.

Results

Population description

All of the 30 subjects were randomized. Twenty-nine subjects completed the study and one subject stopped prematurely between the V1 and V2 visits. In addition to this dropout, during the blind review, data were considered as missing for three subjects for CK analysis, for two subjects for lactate analysis and for one subject with respect to the physical activity score. The number of subjects for which analysis was conducted is indicated in the results tables. The average age, weight and body mass index for each group are detailed in **Table 1**.

	Placebo group (n=15)	**SPro group** (n=15)
Age (years)	21.5 ± 2.4	22.7 ± 5.2
Weight (kg)	75.9 ± 8.5	68.8 ± 9.7
Body mass index (kg/m²)	23.4 ± 2.9	21.9 ± 2.4

Table 1 Descriptive data for the population at V1.
Values are expressed as the mean ± SD

No differences between groups were observed. According to IPAQ-SF analysis, and as expected, no change in exercise habits was observed between groups and between V1 and V2 visits (**Table 2**).

	Placebo group	**SPro group**
V1	2080 ± 786 (n=15)	2241 ± 641 (n=14)
V2 pre-induction	2196 ± 667 (n=14)	2325 ± 820 (n=15)

Table 2 Total scores for physical activity (MET-min/week) according to the IPAQ-SF.
Values are expressed as the mean ± SD

Levels of capillary blood CK

At V2 pre-induction, the levels of capillary blood CK were 136.4 ± 63.7 and 177.1 ± 97.9 IU/l in the SPro and placebo groups, respectively. At V2 post-induction, in the SPro group, the increase in the levels of capillary blood CK after the pain induction protocol was only 10.5 IU/l whereas the increase for the placebo group was 35.7 IU/l (**Table 3**), corresponding to a 70% less increase in the active group compared to the placebo group. The difference between groups was significant (p=0.017).

	Placebo group (n=13)	**SPro group** (n=13)
V2 pre-induction	177.1 ± 97.9	136.4 ± 63.7
V2 post-induction	212.8 ± 118.1	146.9 ± 71.9
Delta	35.7 ± 28.9	10.5 ± 20.6
	p=0.017	

Table 3 Levels of capillary blood CK (IU/l).
Values are expressed as the mean ± SD

Levels of capillary blood lactate

At V2 pre-induction, the levels of capillary blood lactate were 1.9 ± 0.4 mmol/l and 2.5 ± 1.1 mmol/l in the SPro and placebo groups, respectively. At V2 post-induction, the levels of blood lactate increased in a similar way in both groups, by 8.0 and 6.8 mmol/l in the active and placebo groups, respectively. No statistical difference was observed between groups.

Muscular power capacity score

The muscular power capacity scores were first compared with vertical elasticity. At V2 pre-induction, the muscular power capacity scores

were 30.5 ± 5.9 and 31.2 ± 4.8 cm in the SPro and placebo groups, respectively. At V2 post-induction, in the SPro group, the reduction in the muscular power capacity score after the pain induction protocol was only 1.1 cm, whereas the decrease for the placebo group was 2.3 cm (**Table 4**), corresponding to a 52% less decrease in the active group compared to the placebo group. The difference between groups was borderline significant (p=0.086).

	Placebo group (n=14)	**SPro group** (n=15)
V2 pre-induction	31.2 ± 4.8	30.5 ± 5.9
V2 post-induction	28.9 ± 5.2	29.4 ± 4.9
Delta	-2.3 ± 2.1	-1.1 ± 1.5
	p=0.086	

Table 4 Scores for muscular power capacity measured by vertical elasticity (cm).
Values are expressed as the mean ± SD

Power was also measured during this test using the accelerometer placed on the subjects' hips. At V2 pre-induction, the muscular power capacity scores were 45.6 ± 4.0 and 50.7 ± 8.3 W/kg in the SPro and placebo groups, respectively. At V2 post-induction, in the SPro group, the decrease in the muscular power capacity score after the pain induction protocol was only 3.2 W/kg, whereas the decrease for the placebo group was 6.4 W/kg (**Table 5**), corresponding to a 50% less decrease in the active group compared to the placebo group. The difference between groups was borderline significant (p=0.092).

	Placebo group (n=14)	**SPro group** (n=15)
V2 pre-induction	50.7 ± 8.3	45.6 ± 4.0
V2 post-induction	44.4 ± 7.6	42.4 ± 6.0
Delta	-6.4 ± 5.7	-3.2 ± 3.9
	p=0.092	

Table 5 Scores for muscular power capacity measured using an accelerometer (W/kg).
Values are expressed as the mean ± SD

Questionnaire

Analysis of the questionnaire (**Fig.1**) showed that in the SPro group, 13/15 volunteers (87%) positively assessed the product efficacy with respect to performance, whereas this figure was 9/14 (64%) for the placebo group. 9/15 (60%) volunteers said that they were in better physical condition in the SPro group, whereas this figure was only 4/14 (29%) in the placebo group. Finally, 10/15 (67%) volunteers in the SPro group felt less muscle soreness after practising their usual sport discipline, whereas only 6/14 (43%) reported likewise in the placebo group.

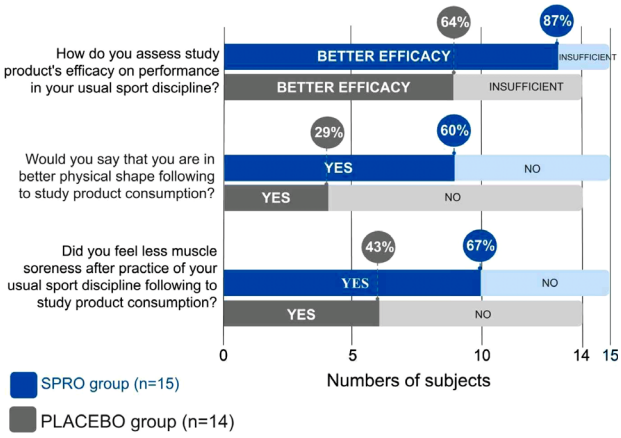

Figure 1 Self-evaluation questionnaire.

Discussion

The results of this pilot clinical study showed the effects of SPro on muscle recovery after physical exertion, when consumed at a dose of 135 mg per day for 12 days.

The follow-up information from the groups confirmed that there were no significant differences at baseline between groups with respect to age, weight and BMI parameters and that the levels of physical activity did not change in either group during product consumption.

SPro significantly reduced the CK release induced by the pain protocol, whereas no significant effect was obtained in terms of blood lactate levels. SPro also limited the decrease

in muscular power capacity induced by the pain protocol, whether measured by vertical elasticity or with an accelerometer.

From a user perspective, the efficacy of SPro was perceived by the subjects to be superior to placebo with respect to performance, physical condition and sensations of muscle soreness. These results reinforce the previous in *vitro* data and highlight SPro as being a promising active complex for muscle protection during physical exertion.

The limitations of this study, such as the small number of subjects and the short duration of product consumption, could explain why only trends were observed in the results of the functional tests, as well as the absence of any effect on lactate levels. For the latter, the results could also be explained by inadequate kinetic measurements. Further investigation with more measuring points on a larger number of subjects should be considered in order to draw more robust conclusions. This is the first time that such a combination of a natural red wine extract, vitamin E and zinc has been shown to have a positive effect on physical exertion in a clinical study.

Some data are already available with respect to testing of the ingredients alone, suggesting that they contribute to the effect.

Indeed, vitamin E has been shown to have a positive effect on markers of muscle damage and soreness. Silva *et al.* [14] showed that vitamin E supplementation brought about an attenuated increase in muscle soreness, lactate dehydrogenase activity, lipid peroxidation and carbonylation compared to placebo, but a similar increase in TNF-α and IL-10 levels was observed. Itoh *et al.* [15] also demonstrated that vitamin E supplementation could reduce the leakage of CK and lactate dehydrogenase following endurance running. Santos *et al.* [16] showed a positive effect of vitamin E supplementation on the reduction of cell damage markers and inflammation after exercise during hypoxic conditions.

Zinc has also been shown to have a positive effect on muscle antioxidant activity in clinical studies. Singh *et al.* [17] demonstrated that supplementation with zinc in male runners blocked the exercise-induced increase in reactive oxygen species. In another study, zinc supplementation prevented an exercise-induced decrease in thyroid hormones and testosterone in sedentary men and could thus be beneficial to performance [18]. Zinc supplementation in healthy adolescent athletes has also been shown to have benefits due to an antioxidant capacity [19]. Kara *et al.* [20] have shown that zinc supplementation in athletes at physiological doses may positively contribute to health and performance.

No clinical study has been conducted on physical recovery and performance using the natural red wine extract tested here. However, other polyphenol-rich ingredients have been widely tested in clinical studies and showed diverging results with respect to muscle protection. As evidenced in the most recent publications, Toscano *et al.* [21] showed that supplementation with a purple grape juice promoted an increased time to exhaustion, accompanied by increased antioxidant activity and a possible reduction in inflammatory markers in recreational runners. A clinical study also showed that a product formulated from mangosteen, pomegranate and elderberry may reduce soreness following eccentric exercise-induced damage [22]. Another formulation derived from grape, pomegranate and green tea was associated with an increase in total power output, maximal peak power output and average power developed, without inducing more fatigue or a higher heart rate [23]. An acute intake of grape and apple polyphenols appeared to enhance the capacity to maintain intensive effort and delay perceived exertion [24].Supplementation with green tea and sour tea had beneficial effects on oxidative stress status in athletes, without an effect on muscle damage indices [25]. Cavarretta *et al.* [26] tested dark chocolate and showed that

its supplementation positively modulated redox status and reduced exercise-induced muscular injury biomarkers in elite football athletes. The findings of Bell *et al.* [27] suggested that Montmorency cherry concentrate was efficacious in accelerating recovery following prolonged, repeat sprint activity. There are also mixed results, such as in the study of Da Silva *et al.* [28], which showed that supplementation with a green tea extract did not reduce the sensation of DOMS, but reduced muscle damage, and so, could have a positive effect on muscle recovery after strenuous exercise. Beyer *et al.* [29] observed that supplementation with a polyphenol blend induced a greater total antioxidant capacity than placebo, but no difference was observed between groups on the following six-week resistance training programme. Furthermore, Lynn *et al.* [30] evaluated bilberry juice consumption in runners completing a half-marathon and observed unexpected results as bilberry juice evoked small to moderate increases in exercise-induced DOMS and C-reactive protein levels.

These clinical studies show that each ingredient could contribute to the promising overall effect observed with SPro, which was demonstrated by the pilot clinical study.

Conclusions

Taking care of our physical fitness through regular physical activity contributes to our overall well-being and happiness. However, physical activity can also induce muscular fatigue, damage and pain, which are brakes to continued practice. That is why facilitating recovery is important, in order to maintain physical activity and performance.

In this pilot clinical study, we have shown that SPro is able to significantly reduce the CK release induced by a physical exercise pain protocol. Moreover, this complex was able to limit the decrease in the muscular power capacity score measured either by vertical elasticity or by power. Lastly, self-evaluation by the subjects demonstrated a greater perceived efficacy for SPro with respect to performance, physical condition and feelings of muscle soreness, compared to placebo.

These results reinforce the data already obtained in *vitro* and highlight SEPIFIT™ Protect as a promising complex to optimize muscle recovery after physical exertion, and thus, to maintain physical activity and performance. Confirmation in a further clinical study with a larger panel of subjects and expanded kinetic measurement is required.

Conflict of Interest

Catherine Kern is co-inventor on a patent filed by Seppic on SPro active ingredient development.

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