

EXTRAMEL® : SOD from melon juice concentrate

Preliminary results of a clinical trial on perceived stress & tiredness

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SUMMARY

The effect of EXTRAMEL® as dietary supplement for signs and symptoms of perceived stress and tiredness was studied in 70 healthy working people using a randomised, double blind, placebo controlled protocol. This study was the first to test an antioxidant enzyme relative to stress on individuals. The study group received 140 IU (NBT) SOD per day and the control group a starch placebo. Perceived stress and tiredness were evaluated through four validated and well-known evaluation scales (FARD, PSS-14, SF-12, Epworth) before supplementation and again 7 and 28 days after supplementation. The improvement of the score at each scales were then compared at D0, D7 and D28 for each group and between groups. The improvement of the main variables was statistically significant in both groups but for several variables, EXTRAMEL® supplementation showed a significantly higher improvement compared to the placebo. Detailed results and discussion allowed to think that EXTRAMEL® has a positive effect on the signs and symptoms of perceived stress and tiredness because of a cognitive and physical tonic action.

INTRODUCTION

In developed countries, people from all social classes are concerned about tiredness, stress and anxiety. It is estimated that 30% of the population will suffer from these symptoms at one point in their life. It is known also that professional activity generates stress and tiredness, which are closely linked.

According to medical sources, the percentage of working people treated for depression is around 10% and people who perceive stress and tiredness is constantly increasing. Today, it is not the pain of physical work anymore which is the main cause of stress and tiredness, but the impact of psychological stress.

To be tired after work is normal. Recuperating easily from physical and psychological tiredness during days off is also normal. But this is a fragile balance which is difficult to maintain. New work modes in an intense global competition context is a powerful generator of stress and tiredness. An important factor to take into account is one's

perceived stress or tiredness and one's own capacity to resist it. An imbalance could lead ultimately to a stage known as the 'burnout syndrome'. Tiredness, stress and anxiety are intimately linked together and are connected.

Moreover, some studies show that there is an emerging link between individual stress and intracellular oxidative stress. Grossi et al demonstrated a correlation between perceived stress and intracellular oxidative stress in a clinical trial on 42 women in the work force. Inflammatory markers like TNF- α or TGF- β were enhanced in women with a high burnout, indicating a role of inflammatory responses and oxidative stress in the pathophysiology of burnout (2). In the same way, Casado et al in a clinical study on workers of a prehospital emergency service, showed a positive correlation between malondialdehyde (MDA), a biomarker of lipid peroxidation and burnout levels (3). Finally, a recent study suggests that cellular oxidative stress seen in mice might be clinically translated as anxious and stressed behaviour in patients (4).

In this context, it seemed interesting to consider a food supplement based on antioxidants that could contribute to the maintenance of the fragile balance between normal tiredness and a negative perception of tiredness leading to the 'burnout syndrome'.

SOD is the main antioxidant found in living cells and organisms. Known since 1969 (5), SOD was largely studied and used as a local treatment to certain diseases like arthritis (6) or in chronic radiotherapy damage (7). Since 2000, a melon juice concentrate containing high level of SOD has been developed, and its use as a dietary supplement, has been a new subject of interest (8,9). Its antioxidant and anti-inflammatory properties have been demonstrated (10). Muth et al reported, in healthy volunteers, that this melon juice concentrate protected against DNA damage resulting from oxidative stress induced by hyperbaric oxygen (11).

The aim of the present study was to determine if the daily intake of a dietary supplement based on EXTRAMEL® is able to decrease the signs and symptoms of perceived stress and tiredness in healthy subjects.

MATERIALS AND METHODS

The clinical trial was an observational study based on individual evaluation scales. The protocol followed was randomized, double blind and placebo controlled. It was approved by the local ethical committee (Poitiers, France) to be conducted by Dr Thierry Cantin.

Rating scales

In order to evaluate the signs and symptoms of perceived stress and tiredness, it was necessary to explore the neurobehaviour sphere of the subjects but also to know about their own perception of stress and its impact on their quality of life and sleep. Four validated and well-known evaluation scales were then chosen:

1) the **Ferreri Anxiety Rating Diagram (FARD) (12,13)** explores four poles divided in three items:

- Somatic pole (attitude, neurovegetative troubles, pain),
- Relational pole (apprehension, internal tension, difficulty of contact),
- Vigilance pole (irritability, sensorial troubles, sleep troubles) and
- Cognitive pole (concentration, weariness, doubt-indecision),

with a total of 12 questions and a score from 0 to 72;

2) the **Cohen Perceived Stress scale (14)** evaluates the perceived stress during the last two weeks with 14 questions and a score from 14 to 70;

3) the **SF-12® Health Survey (15)** allows to measure eight aspects of the quality of life : general physical and mental health state, physical and social functioning, physical and emotional health, pain and vitality. The SF-12 questionnaire is composed of 12 questions with a score from 0 to 12;

4) the **Epworth Sleepiness Scale (16)** is a questionnaire intended to measure daytime sleepiness composed by eight questions with a score from 0 to 18.

In order to avoid the inclusion of depressive subjects, a fifth scale was used for the screening of the volunteers. The **Beck Depression Inventory (BDI) (17)**, a 13 question multiple choice self-report inventory that is one of the most widely used instruments for measuring the severity of depression.

Subjects

A call for volunteers was made in the region of the investigation centre. The pre-inclusion of volunteers was made by the investigator based on:

- **inclusion criteria** to be between 30 to 55 years old, to have a BMI (Body Mass Index) ≤ 30 , to have a stable professional activity for more than one year, to perceive stress & tiredness, to be in full health, not taking any drugs or dietary supplements, not taking tisane or drinks for anti-stress or anti-tiredness;
- **excluding criteria** to be pregnant or breast-feeding, to have a previous case of psychiatric disease, to have pathologies on going or active during the last month, to have received medical treatment (allopathic or homeopathic) during the previous month, to have taken a dietary supplement during the last month, to be in a stressful situation during the next month (wedding, birth, scheduled hospitalisation, important exam...).

After pre-inclusion, volunteers were screened using the fifth evaluation scales.

After screening, 70 volunteers were then included and used as the subjects of our clinical trial. Participation in the study was based on informed consent.

Method of screening the volunteers

Axes were determined by combining the different scales :

- Physical Axis composed by FARD somatic pole (0 – 18), FARD vigilance pole (0 – 18) and SF-12 scale (0 – 12) with a total score from 0 to 48;
- Cognitive Axis composed by FARD cognitive pole (0 – 18) with a total score from 0 to 18;
- Relational Axis composed by FARD relational pole (0 – 18) with a total score from 0 to 18;
- Perceived Stress Axis composed by Epworth sleepiness scale (0 – 18) and Cohen's PSS-14 perceived stress scale (14 – 70) with a total score from 14 to 88.

To be included, the volunteers had to get scores within the following parameters :

- BDI < 5
- Physical Axis > 15/48
- Cognitive Axis > 5/18
- Relational Axis > 5/18
- Perceived Stress Axis > 33/88

The means of each score for the subjects were:

- Physical Axis = 24,95
- Cognitive Axis = 6,27
- Relational Axis = 5,89
- Perceived Stress Axis = 40,7

Treatment protocol

The subjects assigned by randomisation in two groups of 35 were given a food supplement or placebo for 28 days: one capsule per day taken in the morning.

The capsules were indistinguishable and were administered in a double blind approach.

The subjects were tested three times during a visit to the doctor. The first time was before the supplementation (D0), corresponding to the screening evaluation. A test was planned 7 days (D7) after taking the supplement and another one at the end of the trial (D28). The evaluation scales were filled out by the subjects themselves.

During every consultation, the doctor made a general clinical exam (arterial tone and cardiac frequency measure) and filled up an event journal with remarks on the subjects, eventual undercurrent effects, the eventual pathologies and their associated treatment.

Preparation and formulation of the food supplement

The dietary supplements given to the subjects were small hard capsules combining 10mg EXTRAMEL® microgranules (supplied by BIONOV, France) (equivalent to 140 IU of SOD) and starch for the *verum* (EXT) and starch only for the *placebo* (P).

EXTRAMEL® is a freeze-dried melon juice concentrate obtained by physical treatment (crushing the melon, recovery of the pulp, centrifugation, filtration, freeze-drying) of a specific variety of melon which contain a high level of SOD.

As SOD is very sensitive to oxygen, high temperature and acidity, EXTRAMEL® have to be protected. The grade named EXTRAMEL® microgranules correspond to EXTRAMEL® protected by palm oil. Palm oil allows to protect SOD from gastric acidity and then to reach the intestinal tract.

Statistical analysis

The data was expressed as means \pm SD of the evolution of the scores on each scale between D0 and D7 and between D0 and D28 in absolute and relative values.

The paired Student's t-Test (* = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$) were used to analyse each group relative to the amplitude of variation between D0 and D7 and D0 and D28 and to compare results between groups at D0, D7 and D28.

RESULTS

FARD scale

The statistical analysis on Somatic, Vigilance and Cognitive poles showed that scores of these poles were significantly improved at D28 in both groups (*Fig 1*). This clearly indicates that an important placebo effect is present in the study. Nevertheless, when the scores of the groups are compared at D28, a significant difference between them appears: the three poles are much more efficiently improved in the EXT group than in the P group (*Fig 2*) with respectively 18% more for the Somatic pole, 25% more for the Vigilance pole, and 20% more for the Cognitive pole.

Concerning the Relational pole, its improvement is not significant in either group.

Figure 1 : Comparison of the scores of FARD scale poles between EXT and placebo groups before and after EXTRAMEL® supplementation

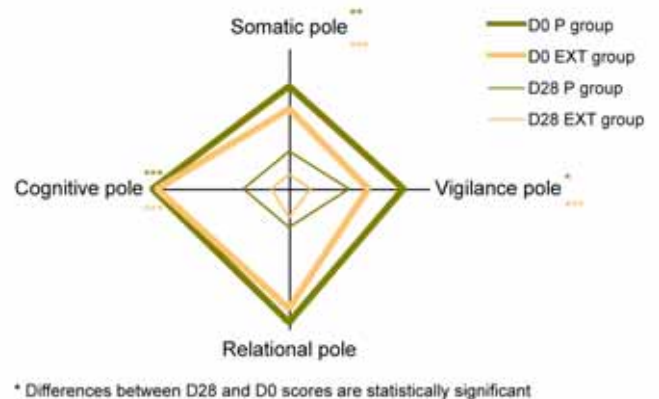
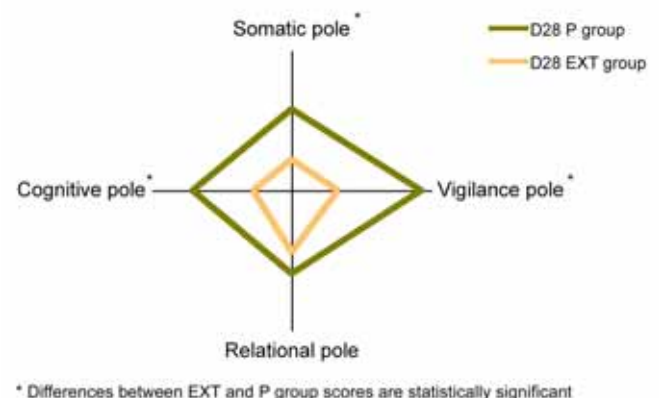


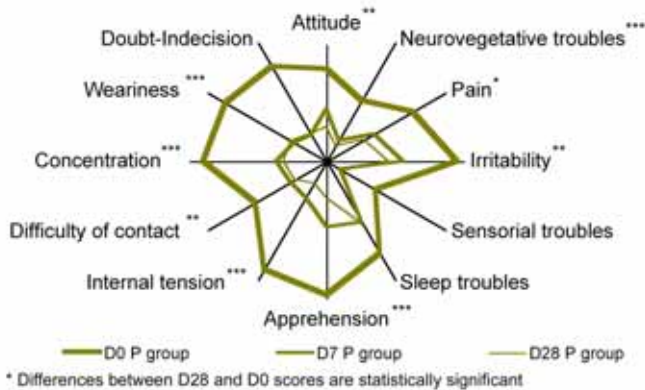
Figure 2 : Comparison of the scores of FARD scale poles between EXT and placebo groups after EXTRAMEL® supplementation



The further analysis of each pole also gave interesting results.

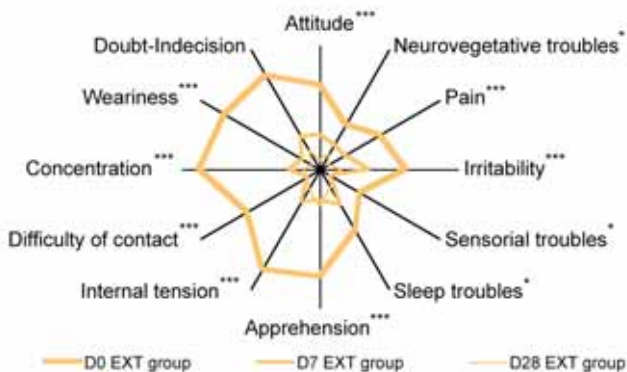
In the P group, all items were significantly improved from D7 excluding Sleep troubles and Doubt-indecision (*Fig 3*).

Figure 3 : Comparison of the scores of FARD scale items for placebo group before, during and after EXTRAMEL® supplementation



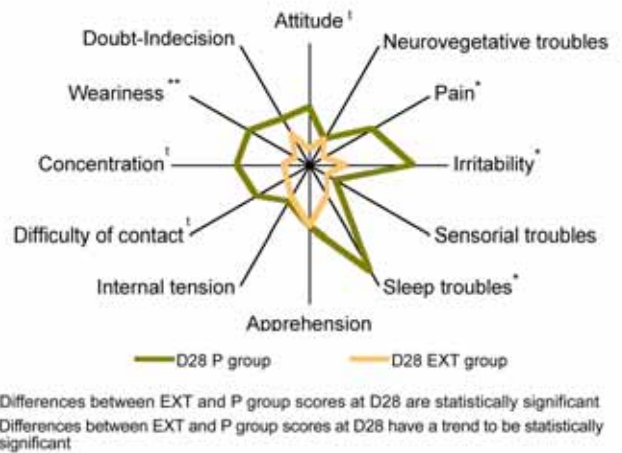
In the EXT group, all items were also significantly improved from D7, excluding only Doubt-indecision, but contrary to the P group, the improvement of certain items continued to increase in D28 (Fig 4).

Figure 4 : Comparison of the scores of FARD scale items for EXT group before, during and after EXTRAMEL® supplementation



At D28, the results (Fig 5) showed that the Pain, Irritability, Sleep troubles and the Weariness scores were significantly improved in the EXT group as compared to the P group, being respectively, 30, 22, 38 and 26% higher. The Attitude, Difficulty of contact and Concentration items also tended to be significantly more improved in the EXT group than in the P group, being respectively, 26, 26 and 22% higher. All other items (Neurovegetative troubles, Sensorial troubles, Apprehension, Internal tension and Doubt-indecision) scores were not significantly different at D28 between the EXT and P groups, and seemed then to be only improved by a placebo effect.

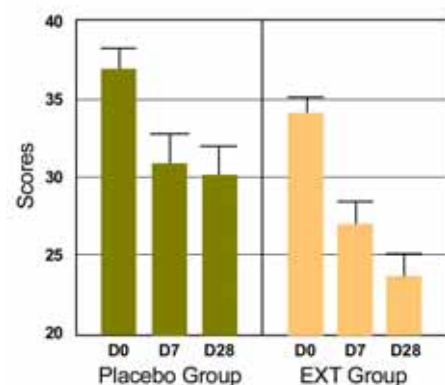
Figure 5 : Comparison of the scores of FARD scale items between EXT and placebo groups after EXTRAMEL® supplementation (D28)



Perceived stress scale

The analysis of the results of the PSS-14 scale (Fig 6) showed that a significant decrease in perceived stress occurred between D0 and D7 in both groups. However, after D7, in the P group, the placebo effect seemed to have reached its maximum level and perceived stress ceased to decrease, whereas in the EXT group, perceived stress continued to decrease with a statistically significant improvement of 12% (p=0.01) compared to the P group at D28 and a global decrease of 30%.

Figure 6 : Scores of PSS-14 scale (Mean ± SD) before, during and after EXTRAMEL® supplementation

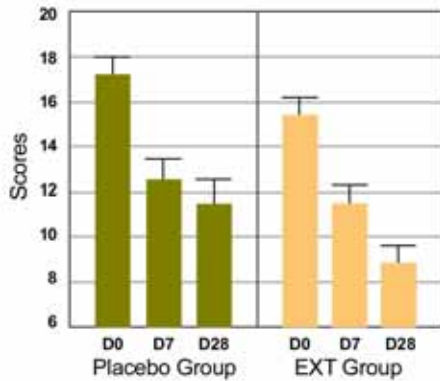


Quality of life scale

The analysis of the results of the SF-12 scale (Fig 7) showed that a high and significant improvement in the quality of life occurred between D0 and D7 in both groups. However, after D7, in P group the placebo effect seemed to have reached its maximum level and the score stopped to decrease whereas in the EXT group, the quality of life continued to improve with a statistically significant difference of 9% (p=0.049) compared to

the P group at D28 and a global improvement of 42%.

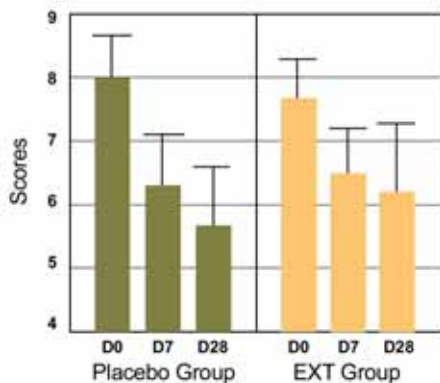
Figure 7 : Scores of SF-12 scale (Mean \pm SD) before, during and after EXTRAMEL® supplementation



Sleepiness scale

The analysis of the results of the Epworth's scale (Fig 8) gave non significant difference between the P and EXT groups.

Figure 8 : Scores of Epworth's scale (Mean \pm SD) before, during and after EXTRAMEL® supplementation



CONCLUSIONS

The FARD scale showed that the signs and symptoms linked to psychological behaviour (neurovegetative and sensorial troubles, internal tension and doubt-indecision) were not improved over the placebo effect whereas signs and symptoms linked to performance, even physical (pain, sleep troubles), cognitive (concentration, weariness, sleep troubles) or behaviour (attitude, irritability, difficulty of contact), were visibly improved with the use of EXTRAMEL® supplementation compared to placebo. Perceived stress and quality of life were also improved by EXTRAMEL® supplementation compared to the placebo whereas no improvement was shown on sleepiness.

DISCUSSION

Tiredness and stress were not very high and corresponded to a normal everyday level of tiredness and stress of working people in developed countries.

Because of this low base level of stress and tiredness, the placebo effect seemed to be very high whereas with a higher base level the difference between EXTRAMEL® supplemented and placebo groups might be more significant. Nevertheless the study highlighted that the placebo effect was only present during the first 7 days of supplementation and not beyond.

It was interesting to note that, despite the high placebo effect and the low base level of stress and tiredness of the subjects, the study highlighted that EXTRAMEL® supplementation had a significantly higher effect compared to placebo on most of the variables of the study and tended to have a significantly higher effect on some others. This may indicate that EXTRAMEL® supplementation has an effect on signs and symptoms of stress and tiredness such as pain, irritability, sleep troubles, weariness, perceived stress and quality of life, covering physical and mental health; moreover it has a probable effect on others such as attitude, concentration and difficulty of contact; and it has no effect on signs and symptoms linked to relational behaviour and sleepiness.

Finally, it was interesting to discover that EXTRAMEL® supplementation has a significant effect on sleep troubles but not on sleepiness, which could be a side effect of many sedatives. This result added to the positive results on perceived stress, quality of life (physical and mental health) and overall physical and cognitive performances could suggest that EXTRAMEL® supplementation acts as a cognitive and physical tonic.

In conclusion, this first trial highlights that EXTRAMEL® supplementation could have a positive effect on several signs and symptoms of stress and tiredness, perceived stress and quality of life as well as on some aspects of neurobehaviour. A second clinical trial should be specifically targeted to study the effects of EXTRAMEL® supplementation on these particular signs and symptoms in order to better understand its action on stress and tiredness.

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