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RESEARCH ARTICLE

A 12-week randomized double-blind parallel pilot trial of Sinetrol XPur on body weight, abdominal fat, waist circumference, and muscle metabolism in overweight men

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Abstract

Overweight and obesity are associated to increased risk of developing non-communicable diseases that might dramatically affect life expectancy according World Health Organization. Overweight, obesity, and decline in physical activity are correlated to a significant propensity to lose skeletal muscle mass as a result of prolonged inflammation and oxidative stress whereas cohort surveys and clinical investigations have demonstrated health benefits of *Citrus*-based polyphenols to reverse such regression. Overweight men were included in a double-blind, randomized, parallel pilot trial where they received daily for a 12-week period 900 mg of a *Citrus*-based polyphenol extract, Sinetrol® XPur. Body composition, anthropometric, and blood parameters were assessed before and at the end of the intervention period. After 12 weeks, while the silhouette slimmed down, metabolic parameters were significantly improved and skeletal muscle catabolism held back. These data suggest that over a 12-week period, the efficacy of the supplement improve both overweight process and correlated skeletal muscle mass metabolism.

Keywords

Abdominal fat, inflammation, insulin resistance, obesity, polyphenols, weight loss

History

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Introduction

Excessive body weight is currently the most common chronic health problem worldwide and one of the greatest public health challenges of the twenty-first century. The etiology of overweight is rooted in cumulative habitual concerns, including imbalanced diets and sedentary behaviors. In addition to causing various physical disabilities and psychological problems, overweight and obesity drastically increase a person's risk of developing a number of non-communicable diseases (NCDs) (Aballay et al., 2013; Balkau et al., 2007b; Cardoso-Saldana et al., 2010; Janus et al., 2007; Kaysen et al., 2009; Wadden & Phelan, 2002) including metabolic syndrome (MS), cardiovascular diseases (CVDs), and type 2 diabetes mellitus (T2DM), which dramatically affect average life expectancy, making overweight and obesity the fifth leading risk factor for global death (World Health Organization, 2013). Nevertheless, overweight and obesity and their consequences are preventable.

Overweight and obesity are defined as abnormal fat accumulation that may impair health, especially when disproportionate fat is stored in the abdominal segment, as it is during the development of MS (Balkau et al., 2007a). Therefore, measuring the abdominal adiposity ratio is considered as the reference method for studying overweight and obesity. Anthropometric measurements such as body mass index (BMI) or waist and hip circumference are generally the most commonly used indicators to assess overweight or obesity (Mushtaq et al., 2011; Singh et al., 1998). However, these markers should be considered as a rough guide because they may not correspond to the same degree of fatness in different individuals. Hence an accurate measurement of abdominal adiposity ratio seems to be more suitable.

In addition to reflecting overweight or obesity, excessive abdominal fat is generally well associated with surrogate biomarkers involved in chronic and low-grade inflammation (Fain, 2010), oxidative stress, and the development of insulin resistance, which are all directly linked to an increased incidence of various clinical NCDs (de Ferranti & Mozaffarian, 2008; Festa et al., 2001; Furukawa et al., 2004; Rodriguez-Rodriguez et al., 2009; Zhang & Zhang, 2010). Accordingly, there is no sudden departure from healthiness to illness in the development of NCDs. Following a generally slight transition, starting without biochemical dysfunctions or other clinical signs, cumulative deviations might lead to a diminishment in well-being and lack of vigor, more or less rapidly before illnesses are confirmed (Stewart & Brook, 1983; Wadden & Phelan, 2002; Wadden & Stunkard, 1985). Consequently, reducing abdominal fat mass and associated metabolic disorders appear as clear and crucial targets for the prevention of excess weight-related manifestations of NCDs (Shen et al., 2009). However, during abdominal fat accumulation throughout the progression of overweight or obesity, it was reported that various metabolic effects associated with age-related changes in body composition and a decline in physical activity were involved with a significant propensity to lose skeletal muscle mass (SMM) (Kim et al., 2014). In addition, several authors observed a significant reduction of SMM in response to a modified diet during weight loss intention in overweight

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populations with excessive abdominal fat (Janssen & Ross, 1999; Ross et al., 1996). Preserving SMM consequently appears to be essential when individuals with a medium- to long-term history of overweight or obesity decide to start a weight loss program.

Sinetrol® XPur is a food-based ingredient product inspired by the Mediterranean diet and designed to provide a synergistic fingerprint of various naturally occurring bioactive components from Citrus; mainly polyphenols in the family of flavanones. Polyphenols from Sinetrol® XPur have previously been shown to enhance weight loss and decrease the abdominal adiposity ratio through the induction of lipolysis (Dallas et al., 2008, 2014); a catabolic process leading to the breakdown of triglycerides (TG) into non-esterified fatty acids (NEFAs) inside adipocytes (Wasserman, 1965).

Based on the rationale of inducing lipolysis, the present study endeavored to demonstrate the health benefits of Sinetrol® XPur in supporting overweight men volunteers to lose significant body weight and reduce the abdominal adiposity ratio while preserving the metabolism of their SMM during a 12-week, balanced normocaloric dietary program.

Material and methods

Subjects

Twenty-five overweight men volunteers with moderate metabolic deviations, but otherwise healthy, were recruited by RDVC Produits Santé, at Le Havre, France, after they agreed to sign a written informed consent form.

Inclusion criteria

Inclusion criteria incorporated overweight men, aged 30–45 years, with a body mass index (BMI) within the range of 26–29.9 kg/m^2 and the prerequisite criteria for the diagnosis of MS, defined as a waist circumference equal to or greater than 94 cm, according to the International Diabetes Federation (IDF) (Alberti et al., 2005).

Subjects who in the previous 6 months were enrolled in a restricted diet for a weight loss program or took weight loss medications or any dietary supplements were not eligible. Exclusion criteria comprised history of weight-reducing surgery, eating disorders, circulation weaknesses or hypertension, chronic allergic or metabolic diseases, stress or anxiety disturbances, and a high rate of either alcohol consumption or smoking. Mean values for central anthropometric characteristics of subjects participating in this study were as follows: waist circumference, 98.6 ± 3.4 cm; hip circumference, 105.1 ± 4.2 cm; body weight, 87.8 ± 5.5 kg; and abdominal adiposity ratio, 26.8 ± 3.3%.

Experimental design

The study was approved by a French Ethical Committee for human experimentation and was conducted according the Good Clinical Practice guidelines of the International Conference on Harmonization of technical requirements for registration of pharmaceuticals for Human use in harmony with the Declaration of Helsinki and in accordance with French drug laws.

A 12-week, double-blind, randomized [1:1] and parallel clinical pilot trial was conducted. Once enrolled, subjects were assigned to one of the two groups, with one receiving placebo ($n = 13$) and the other ($n = 12$) Sinetrol® XPur. Subjects were instructed to take one capsule in the morning at breakfast and one at lunchtime every day for 12 weeks. Participants reported to the research center four times during the 12-week intervention study: at baseline (W0), at week 4 (W4), week 8 (W8), and at the end of the intervention period (W12).

Test treatment

Sinetrol® XPur was obtained by alcohol and/or water extraction from specific varieties of grapefruit (*Citrus paradisi* Macfad.), sweet orange (*Citrus sinensis* L. Osbeck), guarana (*Paullinia cupana* Kunth), and blood orange (*Citrus sinensis* L. Osbeck). Sinetrol® XPur provided polyphenols, mainly flavanones, of which naringin and hesperidin are, respectively, leading markers of grapefruit and both sweet orange and blood orange. It also supplied caffeine from an extract of guarana. The placebo was 100% maltodextrin, which is polyphenol and caffeine free. Each pill contained 450 mg of either Sinetrol® XPur or placebo.

Diet and exercise

The daily energy intake level was recommended at 110–125% of the basal metabolic rate (BMR) according to the revised Harris–Benedict equation (Roza & Shizgal, 1984) which corresponds to 2200–2500 kcal/d. For the whole duration of the study, all subjects were instructed to have 30 min per week of physical exercise.

Determination of anthropometric, vital, and nutritional parameters

Anthropometrics (body weight, waist, and hip circumference), blood pressure, and heart rate were monitored at each visit. For body weight (kg) measurements, subjects wore light clothing at each visit. Waist circumference (cm) was measured at the narrowest point between the lowest rib and the iliac crest using a non-stretchable tape. Hip circumference (cm) was taken around the maximum circumference of the buttocks. Total abdominal adiposity ratio (%) was measured by the ViScan™ system (Tanita Corporation, Tokyo, Japan) at W0 and at W12 (Cases et al., 2014).

Blood analysis

Subjects were sampled for blood after an overnight fast at W0 and at W12. Blood samples were prepared and stored appropriately prior to analyses by enzymatic and colorimetric methods with reagents (Randox, Northern Ireland, UK) on a Hitachi 717 Chemistry Analyzer (Hitachi Inc., Itabashi-ku, Japan) for the following parameters in plasma: metabolic parameters – non-esterified fatty acids (NEFAs), apo-lipoprotein A1 (Apo A1) and glucose; catabolic parameters – uric acid and creatinine; inflammatory markers – fibrinogen and high-sensitivity c-reactive protein (hs-CRP); oxidative status – malondialdehyde (MDA); renal function – urea, sodium (Na), and potassium (K).

Well-being questionnaire

An in-house questionnaire was developed to subjectively assess overall satisfaction with regard to the treatment at W12. The questionnaire was based on the rating of three items: overall satisfaction; perception of greater energy; and perception of well-being. Subjects were requested to score each item on a 0–10 rating scale with 0 for extremely unsatisfied and 10 for extremely satisfied.

Statistics

Statistical analyses were performed using Statview software version 4.51.1 (Abacus Concepts, Berkeley, CA). The data are expressed as mean ± standard deviation (SD). A Kolmogorov–Smirnov test for normality and a Bartlett test for homogeneous variance were performed for each group. Changes within and between groups at W0 and W12 for the clinical and laboratory parameters were analyzed using unpaired Student's *t*-test.

Results of the questionnaire were analyzed with the Wilcoxon rank test. A minimum value of $p<0.05$ was selected as the threshold for statistical significance.

Results

Anthropometric results and body composition

Before the onset of the intervention period (W0), body weight, abdominal body fat, and anthropometric parameters were similar in the placebo and Sinetrol® XPur groups (Table 1). Percent changes in waist and hip circumference and body weight began to show significant differences between the placebo and Sinetrol® XPur groups from week 4 for the former and week 8 for the latter (data not shown).

After 12 weeks of treatment, percent decreases in waist and hip circumference, abdominal body fat, and body weight in the Sinetrol® XPur group were greater than those of the placebo group (Table 1). The waist reduction was 7.5% for the Sinetrol® XPur group versus 2.1% for the placebo group ($p<0.001$), corresponding to a mean reduction in waist circumference of 7.4 cm versus 2.1 cm, respectively. Hip circumference decreased by 5.3% in the Sinetrol® XPur group compared with 1.9% for placebo, corresponding to mean reductions of 5.6 cm and 2.0 cm, respectively ($p<0.001$).

The waist-to-hip ratio in the placebo group at baseline and W12 was 0.93, and 0.95 and 0.92 in the Sinetrol® XPur group at W0 and W12, respectively. In the placebo group, the ratio variation (Δ%) showed no change during the study, whereas it significantly decreased by 2.3% in the Sinetrol® XPur group ($p<0.05$).

At W12, abdominal body fat was decreased by 9.7% in the Sinetrol® XPur group, whereas the decrease was 4.8% in the placebo group, with a highly significant difference between the two groups ($p<0.001$). Body weight decreased by 3.7% in the Sinetrol® XPur group versus 1.8% in the placebo group ($p<0.001$), corresponding to a loss of 3.4 kg versus 1.5 kg, respectively.

Metabolic parameters

Between the placebo and Sinetrol® XPur groups, blood NEFAs, Apo A1, and glycemia levels showed no difference at the beginning of the study (Table 2) and were in the normal range, i.e. <5.6 mmol/L (glycemia), <720 µmol/L (NEFAs), and 37–77 µmol/L (Apo A1), respectively.

Glycemia was not modified between W0 and W12 in the placebo group, whereas it was reduced by 13.6% ($p<0.05$) in the Sinetrol® XPur group. The level of NEFAs increased in both groups ($p<0.05$, Table 2) at W12. However, the increase in the Sinetrol® XPur group (+274%) was significantly greater than that of the placebo group (+20%; $p<0.001$). Apo A1 increased in the Sinetrol® XPur group by 5.4% whereas it decreased by 3.3% in the placebo group ($p<0.05$).

Renal function and muscle mass metabolism

Kidney function was assessed through plasma K, Na, and urea levels, which were not affected and remained within the normal healthy range throughout the 12 weeks of treatment in both the Sinetrol® XPur and placebo groups (Table 3).

The level of creatinine increased by 15.7% in the placebo group, reaching the upper healthy limit, whereas no significant change occurred in the Sinetrol® XPur group. The MDA level, within normal range in the placebo group at baseline, significantly increased by 14.8% ($p<0.05$), which was beyond the upper limit of the healthy range, whereas it tended to decrease ($p=0.0689$) in the Sinetrol® XPur group. Muscle inflammatory markers, such as levels of hs-CRP and fibrinogen, showed no differences between the placebo and Sinetrol® XPur groups at W0. At W12, while no changes occurred for fibrinogen in the placebo group, hs-CRP was significantly increased by 16.7% ($p<0.05$). The same parameters significantly decreased at W12 in the Sinetrol® XPur group, respectively, by 14.7% ($p<0.05$) and 46.7% ($p<0.05$). Similar to the level of fibrinogen, the level of uric acid decreased by 17.8% ($p<0.001$) after 12 weeks of treatment with Sinetrol® XPur (Table 3).

Tolerance

During the course of the study, there were no signs of metabolic disturbances among the volunteers, as indicated by preserved renal function (Table 3) and liver enzymes (ALT, ASAT, and g-GT) (data not shown). Neither adverse events nor side effects were reported by the investigator. In the in-house subjective

Table 2. Blood metabolic parameters at baseline (W0) and after 12 weeks (W12) of treatment with placebo or Sinetrol® XPur in healthy overweight male adults.

	Placebo		Sinetrol® XPur	
Normal range	W0	W12	W0	W12
Glycemia (mmol/L) <5.6	6.1 ± 0.5	6.1 ± 0.3	5.9 ± 0.6	5.1 ± 0.5[a]*
NEFAs (µmol/L) <720	154.6 ± 25.3	186.2 ± 36.8[a]	155.6 ± 19.3	581.3 ± 115.6[a]*
Apo A1 (µmol/L) 37–77	48.2 ± 8.0	46.6 ± 3.5	50.2 ± 9.4	52.9 ± 3.0*

Values are means ± SD, $n=13$ (placebo) or $n=12$ (Sinetrol® XPur). NEFAs, non-esterified fatty acids; Apo A1, apolipoprotein A1. *$p<0.001$ indicates a difference between placebo and Sinetrol® XPur. [a]An intragroup difference between W0 and W12 at $p<0.05$.

Table 1. Weight, abdominal fat, waist size, and hip circumference and % change (Δ) at baseline (W0) and after 12 weeks (W12) of treatment with placebo or Sinetrol® XPur in healthy overweight male adults.

	Placebo			Sinetrol® XPur		
	W0	W12	Δ (%)	W0	W12	Δ (%)
Body weight (kg)	86.4 ± 4.7	84.9 ± 4.7[a]	−1.76 ± 0.61	89.3 ± 6.1	85.9 ± 5.6[a]	−3.75 ± 0.81**
Abdominal fat (%)	26.7 ± 3.3	25.4 ± 2.8[a]	−4.81 ± 1.74	26.9 ± 3.4	24.3 ± 3.3	−9.74 ± 3.84**
Waist (cm)	98.5 ± 3.6	96.4 ± 3.4[a]	−2.11 ± 0.48	98.8 ± 3.3	91.4 ± 3.5[a]	−7.50 ± 2.00**
Hip (cm)	105.5 ± 4.0	103.5 ± 4.0[a]	−1.89 ± 1.24	104.7 ± 4.5	99.1 ± 4.5[a]	−5.33 ± 1.68**
Waist/hip ratio	0.93 ± 0.02	0.93 ± 0.02	−0.20 ± 1.53	0.95 ± 0.04	0.92 ± 0.04[a]	−2.27 ± 2.42*

Values are means ± SD, $n=13$ (placebo) or $n=12$ (Sinetrol® XPur). Δ (%): % difference W12–W0. *$p<0.05$ and **$p<0.001$ indicate Δ differences between placebo and Sinetrol® XPur.
[a]An intragroup difference between baseline and W12 at $p<0.05$.

Table 3. Muscle metabolism and kidney function at baseline (W0) and after 12 weeks (W12) of treatment with placebo or Sinetrol® XPur in healthy overweight male adults.

	Placebo		Sinetrol® XPur	
Normal range	W0	W12	W0	W12
Muscle metabolism				
Creatinine (mg/L) 9–14	12.1 ± 2.4	14.0 ± 1.9[a]	12.4 ± 1.7	13.3 ± 2.2
Inflammation				
hs-CRP (mg/L) <5	2.4 ± 1.4	2.8 ± 1.2[a]	3.0 ± 1.7	1.6 ± 0.7[a]
Fibrinogen (g/L) 1.5–3	3.5 ± 0.7	3.5 ± 0.7	3.4 ± 0.8	2.9 ± 0.5[a]*
Oxidative stress				
MDA (μmol/L) <2.8	2.7 ± 0.3	3.1 ± 0.3[a]	3.2 ± 0.4	2.9 ± 0.5
Uric acid (mg/L) 40–60	56.5 ± 10.0	58.8 ± 5.2	58.3 ± 6.4	47.9 ± 4.1[a]**
Kidney function				
Na (mmol/L) 135–145	134.6 ± 3.3	135.4 ± 4.6	136.2 ± 2.4	135.6 ± 2.7
K (mmol/L) 3.6–5.2	4.0 ± 0.3	3.9 ± 0.2	4.3 ± 0.3	4.5 ± 0.4**
Urea (g/L) 0.18–0.45	0.44 ± 0.05	0.45 ± 0.05	0.36 ± 0.12	0.41 ± 0.08

Values are means ± SD, $n = 13$ (placebo) or $n = 12$ (Sinetrol® XPur). *$p < 0.05$ and **$p < 0.001$ indicate a difference between placebo and Sinetrol® XPur.
[a]An intragroup difference between W0 and W12 at $p < 0.05$.

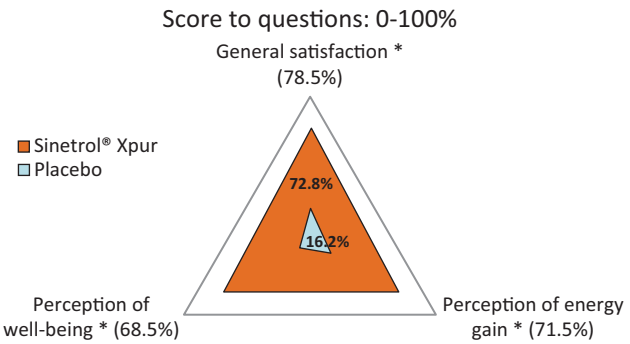

Figure 1. Perception of Sinetrol® XPur efficacy after 12 weeks of supplementation. Values are means, $n = 13$ (placebo) or $n = 12$ (Sinetrol® XPur). *$p < 0.001$ indicates a difference between placebo and Sinetrol® XPur.

questionnaire, all items scored significantly higher values in the Sinetrol® XPur group compared with the placebo group (Figure 1).

Discussion

The present study demonstrates health benefits of a 12-week supplementation with Sinetrol® XPur, a Citrus-based polyphenol extract inspired by the Mediterranean diet, on anthropometric and metabolic parameters of overweight men at risk of developing MS.

MS is the result of a constellation of metabolic deviations that increase an individual's risk for the occurrence of NCDs, mainly CVDs and DMT2. Despite the existence of several official definitions for MS, they all agree that resistance to insulin is a key feature generally resulting from a higher prevalence for individuals with excessive abdominal obesity (Despres et al., 2008). As a consequence, the IDF introduced excessive abdominal obesity as a prerequisite criterion for the diagnosis of MS, defined as waist circumference equal to or greater than 94 cm for Caucasian men (Alberti et al., 2005). Thus, the targeted population of the present study displayed one recognized risk factor among a mandatory minimum of 3, according to the IDF definition of MS. Consequently, this population might be considered at risk for developing MS, or, as reported by others, a ''pre-metabolic syndrome'' (de las Fuentes et al., 2007; Stagnaro, 2007).

Anthropometric parameters and body composition

In this study, supplementation with Sinetrol® XPur was able to significantly decrease body weight (−3.75%) and abdominal fat deposit (−9.74%), as well as waist (−7.50%) and hip (−5.33%) circumference. These changes were all significantly higher than for the placebo group. It is of further interest to note that after 12 weeks of Sinetrol® XPur, excessive abdominal obesity was sufficiently reversed that it brought volunteers below the limit of risk for MS as defined by the IDF (waist circumference, <94 cm), and that the attending decrease in waist circumference became significant from the fourth week of supplementation (data not shown). Combined with the loss in body weight, highly improved perceptions of well-being, energy-gain, and overall satisfaction, as shown by the results of the questionnaire presented to volunteers at the end of the study, serve to emphasize progress towards a greater state of health. The positive outcomes of the present study are supported by a previous clinical trial (Dallas et al., 2014) conducted in 95 overweight men and women in which a daily supplement of Sinetrol® XPur was demonstrated to significantly decrease body fat, waist, and hip circumference.

Previously, several authors have reported that a decrease in body weight correlated with the consumption of Citrus fruit and/or Citrus fruit-derived polyphenols (Chudnovskiy et al., 2014; Titta et al., 2010). Although the majority of correlating interventions were pre-clinical studies, a clinical investigation (Fujioka et al., 2006) conducted with 91 obese adults clearly demonstrated that consumption of grapefruit, known to be rich in a specific flavanone, naringin, is able to induce significantly higher weight loss (−1.6 kg) than placebo after 12 weeks of supplementation.

Metabolic parameters

Anthropometric benefits highlighted in the present study can be readily attributed to the specific polyphenolic combination, mainly naringin and hesperidin, probably acting synergistically together and with other polyphenols in the product. A previous study (Dallas et al., 2008) demonstrated that a Citrus extract (Sinetrol® EXP) of similar polyphenolic content was able to operate as an efficient fat burner through a lipolytic mechanism involving the inhibition of cAMP-phosphodiesterase (PDE),

resulting in an induced lipolysis as assessed by a significantly higher release of NEFAs in the plasma of treated volunteers. In the present study, volunteers consuming Sinetrol® XPur also displayed a significant increase of NEFAs in plasma, which reached more than three times the level observed in the placebo group. In addition, it should be noted that at baseline, volunteers of both groups failed to exhibit either hypercholesterolemia or hypertriglyceridemia (data not shown), and this lipid profile remained unchanged and within healthy range throughout the study. However, Sinetrol® XPur supplementation resulted in an increase of Apo A1 levels in plasma, which attained a significantly higher level compared with placebo after 12 weeks. Apo A1 is the principal protein component of HDL ensuring the removal of excess cholesterol from tissues for which its protective properties on the cardiovascular system are attributed. A significant increase in Apo A1 concentration has formerly been reported with orange juice intake (Asgary et al., 2014) in healthy volunteers after 8 weeks of regular consumption, while HDL levels remained constant. A previously reported correlation between increased Apo A1 and a lipolytic effect could, in the case of Sinetrol® XPur, be elicited through an increased transcriptional regulation of lipid metabolism, particularly through the peroxisome proliferator-activated receptor (PPAR) pathway (Mulvihill & Huff, 2012). PPARs are nuclear receptor transcription factors controlling and regulating the expression of many genes, including lipid metabolism-based genes (Monsalve et al., 2013). Evidence supporting the mechanism was shown in an *in vitro* study (Goldwasser et al., 2010) in which it was demonstrated that naringenin, the aglycone form of naringin, is an agonist of PPARs, enabling their activation and inducing a ''fasted-like state'' in rat hepatic cells in culture.

Beyond adipose fat deposition in the abdominal segment, another common and central criterion for MS is excessive fasting glycemia. It is now widely accepted that abdominal obesity is strongly associated with hyperglycemia-induced resistance to insulin, resulting at term in the development of DMT2. The unhealthy limit, as defined by the IDF, is a fasting glycemia equal to or greater than 5.6 mmol/L. Regarding the individuals included in the study, although all volunteers might not have been measured below the limit of 5.6 mmol/L, the average fasting glycemia at baseline, 6.0 mmol/L, can nonetheless be considered a pre-diabetic state. Supplementation with Sinetrol® XPur for 12 weeks was able to reverse this metabolic dysfunction toward a normal range (−13.6 % at 5.1 mmol/L), preventing, as a consequence, one of the most important risk factors for MS immediately after excessive abdominal adiposity. Metabolic effects of Citrus fruit on glycemic homeostasis have been well documented in experimental animal models of diabetes. Thus, *db/db* diabetic mice supplemented with naringin or hesperidin at 200 mg/kg for 5 weeks (Jung et al., 2006) displayed a significant decrease in blood glucose levels (−30% and −20%, respectively), which were directly linked to an up-regulation of enzymes involved in the metabolism of glucose. Furthermore, in a study of streptozotocin-induced diabetes in rats (Sharma et al., 2011), oral administration of naringin for 28 d was able to lower hyperglycemia and resistance to insulin, as well as the release of inflammatory cytokines, in a dose-dependent manner. Although the mechanism of action of Citrus polyphenols on glucose homeostasis is not fully understood, it appears that antioxidant effects associated with anti-inflammatory properties would play a primary function similar to an insulin-like effect (Mahmoud et al., 2012). Collectively, these effects are apparently emphasized in the present study with Sinetrol® XPur through its ability to help to regulate glucose homeostasis and at the same time being effective in significantly decreasing markers of inflammation, fibrinogen and hs-CRP, respectively, by 14.7% and 46.7%.

Skeletal muscle catabolism markers

The literature is clear and there are no doubts that markers of inflammation, fibrinogen and hs-CRP, when elevated beyond a normal healthy range, reflect a condition of low grade and most often, chronic inflammation, directly correlated with an excessive deposit of abdominal fat mass (Maury et al., 2010). Hence, weight loss, and particularly a decrease in waist circumference, should be associated with a reduction of inflammatory markers, as others have recently demonstrated (Petelin et al., 2014). Furthermore, it is noteworthy that weight loss interventions have also been associated with an induction of muscle catabolism resulting in a slight but significant loss of SMM (Janssen & Ross, 1999). Among biomarkers for SMM catabolism, urinary excretion of creatinine has been clearly correlated and widely used as the reference marker for assessing SMM variation (Davies et al., 2002). Results obtained in the present study underline a moderate but significant increase of plasma creatinine, despite the fact that renal function appears efficient and unchanged, as observed from values in plasma for K, Na, and urea within the healthy range for the placebo group. This can easily be related to an enhanced SMM catabolism. Such an increase of SMM catabolism was also marked, as previously suggested, by the existence of a low-grade inflammation in the placebo group. The relation between inflammation and SMM catabolism has been highlighted in several clinical trials, mainly in regard to TNF-α, IL-6, or CRP levels (Cesari et al., 2004; Schaap et al., 2006); all inflammatory markers generally recognized to have possible catabolic effects on SMM (Fanzani et al., 2012). While fibrinogen remained constant but beyond the standard healthy range, the placebo group displayed an increase in plasma hs-CRP concentration (+16.7% at week 12), thereby lending further evidence for the role of this additional marker as a probable but partial inductor of SMM reduction during weight loss. Finally, volunteers supplemented with placebo showed an increased MDA level, a typical by-product of lipid peroxidation, pointing out the presence of oxidative stress, probably linked to their overweight condition with excessive deposits of abdominal fat. In an elegant review (Cesari et al., 2012), it was reported that products of oxidative damage were associated with an enhanced SMM catabolism. Sinetrol® XPur-supplemented volunteers, on the contrary, did not appear to display any additional SMM catabolism as assessed by the markers involved. Indeed, creatinine levels were not significantly increased, low-grade inflammation was decreased below the upper limit level, and none of the volunteers in the group exhibited any signs of enhanced oxidative stress. Along the same line, a significant reduction of uricemia was measured within the Sinetrol® XPur group whereas the placebo group had a significantly higher level at the end of the investigation, confirming the possible role of Sinetrol® XPur in the reduction of SMM catabolism, as previously observed with alanine on the decrease of SMM catabolism correlated with a decrease in hyperuricemia in an obese population (Genuth, 1973). These beneficial effects can easily be explained by known antioxidant and anti-inflammatory properties of polyphenols derived from Citrus fruits. Supportive evidence is shown in a recent study (Jain & Parmar, 2011) with a robust *in vivo* model of inflammation, i.e., the rat air pouch model, in which the effects of naringin and hesperidin on oxidative and inflammatory markers were compared. The authors concluded that both flavanones were able to reverse air pouch-induced inflammation, and they proposed that the individual mechanism of action of polyphenols should not be the same: hesperidin would display superior anti-inflammatory effects as highlighted by a decrease in TNF-a while naringin would contribute to an improvement in health through the reduction of oxidative stress, as observed from a significant decrease in plasma

MDA, which is also the case in the present study. Both the level of MDA and inflammation markers were decreased with Sinetrol® XPur, which confirms a synergistic effect of Citrus polyphenols, acting in concert to significantly ameliorate a vicious cycle between the inflammation and the oxidative stress arising from excessive deposits of abdominal fat.

Conclusion

In the present study, Sinetrol® XPur clearly appears to be a natural and safe option for overweight and obese populations. Indeed, supplementation with Sinetrol® XPur was associated with a significantly important decrease of abdominal fat (−9.74%), a profound reduction in waist circumference (−7.50%, corresponding to more than 7.40 cm), and an evident preservation of the SMM during weight loss. The results show a genuine benefit of the product in managing overweight and obesity-linked metabolic disturbances, which could deter and prevent the development of MS in individuals at risk. Nevertheless, further investigations of the mechanisms of action of Citrus polyphenols in relation to their respective bioavailabilities need to be conducted in order to gain a better understanding of their beneficial effects on the modulation of body composition.

Declaration of interest

Fytexia is involved in the research, development, marketing, and sales of polyphenolic extracts from various fruit and vegetables regularly consumed within the Mediterranean diet for food and nutraceutical industries. Therefore, Fytexia has a commercial interest in this publication. RDVC was paid by Fytexia to conduct the clinical investigation and perform the clinical and biochemical measurements forming the basis of this publication. UMR 204 NUTRIPASS examined raw data to determine health benefits and hypotheses. Fytexia, RDVC, and UMR 204 NUTRIPASS declare that the data in this report represent a true and faithful representation of the work that has been performed. The financial assistance of Fytexia is gratefully acknowledged.

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