

Clinical Study to Assess the Efficacy and Safety of a Citrus Polyphenolic Extract of Red Orange, Grapefruit, and Orange (Sinetrol-XPur) on Weight Management and Metabolic Parameters in Healthy Overweight Individuals

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The present study investigated the efficacy and safety effects of Sinetrol-XPur (polyphenolic citrus dry extract) in weight management; metabolic parameters; and inflammatory, glycemic and oxidative status. In a 12-week, randomized, double-blind, placebo-controlled trial, Sinetrol-XPur was given to overweight subjects twice daily with meals in the tested group ($N=47$) versus a placebo group ($N=48$). Waist and hip circumference and abdominal fat were decreased in the Sinetrol-XPur group as compared with the placebo group ($p < 0.0001$) (-5.71% vs -1.56% for waist, -4.71% vs -1.35% for hip and -9.73% vs -3.18% for fat). Inflammatory markers were reduced (C-reactive protein: -22.87% vs $+61\%$; fibrinogen: -19.93% vs -1.61% , $p < 0.01$). Oxidative stress was lowered as seen by the reduction of malondialdehyde (-14.03% vs 2.76%) and the increase in superoxide dismutase and glutathione (17.38% vs 2.19% and 4.63% vs -2.36% , respectively, $p < 0.01$). No adverse effects were observed. Kidney, liver, and lipid panels remained unchanged. These results indicated that Sinetrol-XPur supplementation is a viable option for reducing abdominal fat, waist and hip circumference, and body weight and for improving inflammatory, glycemic, and oxidative status in healthy overweight individuals. Copyright © 2013 John Wiley & Sons, Ltd.

Keywords: weight management; citrus extract; polyphenols; overweight; inflammation; oxidative stress.

Abbreviations: Apo, apolipoproteins; BMI, body mass index; CRP, C-reactive protein; CV, cardiovascular; FFA, free fatty acid; GSH, glutathione; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MDA, malondialdehyde; SOD, superoxide dismutase; TG, triglyceride

INTRODUCTION

People are becoming fatter worldwide. Recent data show that excess body fat weight is pandemic, with one-half to two-thirds of the population being overweight or obese in 2006. A greater amount of fat, especially found in the abdominal region, increases the risk of CV diseases and type 2 diabetes (Balkau *et al.*, 2007). Indeed, obesity is associated with decreased HDL and increased LDL and TGs, all risk factors for CV diseases (Kaysen *et al.*, 2009).

Furthermore, obesity is associated with low-grade inflammation and chronic inflammatory response characterized by activation of some pro-inflammatory signaling pathways and abnormal production of markers such as fibrinogen and CRP (Fain, 2010).

These molecules are implicated in many clinical manifestations of pathologies such as diabetes, arterial hypertension, or CV diseases (Festa *et al.*, 2001; Rodríguez-Rodríguez *et al.*, 2009; Zhang and Zhang, 2010). Fat accumulation is correlated with elevated markers of oxidative stress, which plays critical roles in the development of impaired insulin secretion, diabetes, and atherosclerosis (Furukawa *et al.*, 2004; De Ferranti and Mozaffarian, 2008). Reducing abdominal fat mass and concomitant oxidative stress could be important targets for the prevention of obesity-related diseases (Shen *et al.*, 2009).

Excess body fat is the primary characteristic of obesity. Therefore, a precise measurement of the percentage body fat is considered the reference method for defining obesity. Anthropometric indices such as BMI, waist circumference, and waist-to-hip ratio are the most commonly used indicators for assessing abdominal obesity (Singh *et al.*, 1998; Mushtaq *et al.*, 2011).

Flavonoids constitute the most important class of polyphenolic compounds, such as anthocyanins (malvidin,

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cyanidin, and petunidin), flavanones (naringin, hesperidin, narirutin, naringenin, etc.), flavan-3-ols (catechin, epigallocatechin, etc.), and flavonols (quercetin and kaempferol). Flavonoids have taken an increasing importance with regard to their health benefits in prevention and treatment of cancer (Chen *et al.*, 2004; Moghaddam *et al.*, 2012; Mansoor *et al.*, 2011; Seito *et al.*, 2011; Yang *et al.*, in press), inflammatory diseases (Laughton *et al.*, 1991; Kim *et al.*, 2012; Dai *et al.*, 2012), CV diseases (Frankel *et al.*, 1993; Moon *et al.*, 2012; Vaidya *et al.*, 2012), and neurodegenerative diseases (Orgogozo *et al.*, 1997; Kou *et al.*, 2011; Zhang *et al.*, 2012). Dietary phytochemicals, such as polyphenols, may prevent the risk of obesity-associated chronic diseases such as type 2 diabetes (Dembinska-Kiec *et al.*, 2008; Décordé *et al.*, 2009). *In vitro* studies have shown that flavonoids possess lipolytic activity via inhibition of cyclic adenosine monophosphate (cAMP) phosphodiesterase (PDE) and maintain lipolysis-inducing cAMP levels (Kuppusamy and Das, 1992; Dallas *et al.*, 2008). Naringenin, for example, which is an aglycone of the grapefruit flavonoid naringin, has been reported to induce the expression of fatty acid oxidation genes *CYP4A11*, *ACOX*, *UCPI*, and *ApoA1*. (Goldwasser *et al.*, 2010). These would support the effect observed in overweight subjects on weight and body fat loss after 12 weeks of daily supplementation (Dallas *et al.*, 2008).

Hence, a food supplement rich in polyphenols that would contribute to the reduction of not only body fat but also inflammatory and oxidative stress status would be of great health value.

Therefore, the aim of this study was to demonstrate that a proprietary polyphenolic-rich combination would help reduce body fat, inflammation, and oxidative stress in healthy overweight subjects, safely and without adverse effects.

MATERIALS AND METHODS

Study design. A 12-week, randomized, double-blind, placebo-controlled clinical trial was conducted in overweight individuals with daily supplementation of a citrus polyphenolic extract (Sinetrol-XPur). The study was conducted at four clinical research sites accredited by a joint commission and by the Haute Autorité de Santé: American Hospital in Paris, Centre Medical, Centre Exploitation Vasculaire, and Centre Exploitation Biologique in Paris. The procedures complied with the ethical standards and approved by the Association National de Prévention des Maladies and Biological Research and Collections (clinical trial registration number 2012-A01702-4).

Subjects. Ninety-five healthy overweight volunteers of both sexes (55 women and 40 men) aged 22 to 45 years, with a BMI of 26–29.9 kg/m² and comparable socioprofessional status (middle class) and sedentarily living in Ile de France, participated in the study.

Exclusion criteria. Subjects taking weight loss medications or dietary supplements or on weight loss programs in the last 3 months and having a history of weight-reducing surgery or an eating disorder were excluded, together with pregnant or lactating women and postmenopausal women. Individuals having high blood

pressure, chronic or allergic metabolic diseases, metabolic syndrome, diabetes, stress diseases, high alcohol consumption, or a known intolerance to one of the components of the tested product were also excluded.

Test compound. Sinetrol-XPur is a proprietary polyphenolic-rich fruit extract (red orange, grapefruit, sweet orange, and guarana). It was standardized to contain at least 90% of total polyphenols (expressed as catechin), at least 20% of total flavanones (expressed as naringin) and between 1% and 3% of natural caffeine.

Total polyphenols, flavanones, and caffeine were measured by high-performance liquid chromatography-ultraviolet (Dallas and Laureano, 1994a, 1994b). The dry extract was packaged in red gelatine capsules (450 mg per capsule). Identical-looking capsules were filled with 450 mg of maltodextrin and used as placebo.

Study protocol. Ninety-five volunteers were randomly assigned into two groups, one receiving placebo ($n=48$) and the other group receiving the active compound (Sinetrol-XPur) ($n=47$) for 12 weeks. Participants received either 180 placebo capsules (packed in a plastic 100-ml closed box) or 180 Sinetrol-XPur capsules (provided by Fytexia), all labeled and coded in such a way that subjects and staffs were unaware which product each participant was receiving.

Subjects were instructed to take one capsule at breakfast and one capsule at lunch for a total of two capsules per day or 900 mg. Subjects were also instructed to keep the original box closed after each use of the capsules. All participants reported to their corresponding research centers four times during the 12-week intervention: at baseline (W0), at week 4 (W4), at week 8 (W8), and at week 12 (W12).

Diet and exercise. The calorie level was set at 1800–2000 kcal/day for women and between 2000 and 2500 kcal/day for men. A brief diet and physical questionnaire were administered to determine usual nutrient intakes and detect any significant changes that may have occurred from the recommended diet. All subjects were instructed to have 30 min/week of physical activity (three sessions of 10-min walk).

Primary outcome variables. The primary outcome variables were changes in mean body weight, BMI, body fat, waist and hip circumference, waist-to-hip ratio, and FFA.

Secondary outcome variables (safety). The secondary outcome variables were changes in blood safety parameters such as blood pressure, heart rate, lipid profile (total cholesterol, HDL, LDL, TG, ApoA1, and ApoB), glucose and hemoglobin A1c (HbA1c), kidney function (Na, K, urea, and creatinine), inflammation markers (fibrinogen and CRP), liver function (alanine, alanine amino transaminase, aspartate amino transaminase, gamma-glutamyl transpeptidase, and creatine phosphokinase), and oxidative status (SOD, MDA, and GSH).

Methods of analysis. Body weight (kg) was measured to the nearest 0.1 kg at each visit with subjects wearing light clothing. Height (cm) was measured using a stadiometer

with subjects barefoot; BMI was calculated (weight/height squared) (kg/m^2). Waist circumference (cm) was measured at the narrowest point between the lowest rib and the iliac crest using a nonstretchable tape. Hip circumference (cm) was taken around the maximum circumference of the buttocks. Total abdominal adiposity was measured by the ViSCAN system (Tanita Corporation, Arlington, IL) at baseline and week 12 (Thomas *et al.*, 2010). Systolic and diastolic blood pressures and heart rate were taken in the supine position after 15-min rest at each visit.

Subjects gave blood samples between 8:30 and 9:30 in the morning after an overnight fast at W0 and at W12. Blood samples were prepared and stored appropriately until they were analyzed by using enzymatic and colorimetric methods (Randox reagents, UK) on Hitachi 717 (Japan) for the safety parameters.

The overall compliance in the study was excellent. One hundred thirteen subjects were screened for eligibility, and 18 subjects were excluded (did not meet inclusion criteria). Ninety-five subjects were enrolled and randomized for the study (48 subjects for the placebo group and 47 subjects for the intervention group (Sinetrol-XPur)). All the subjects (95) completed the study. Subjects' compliance was checked at each visit (W0, W4, W8, and W12) to make sure that they all performed the planned program. Compliance to the protocol was checked by measuring the difference between the numbers of unused capsules and the expected number to be taken.

Statistical analysis. Statistical analyses were performed using STATVIEW software version 4.51.1 (Abacus Concepts, Berkeley, CA). The data are expressed as mean \pm standard deviation. A Kolmogorov–Smirnov test for normality and a Bartlett test for homogeneous variance were performed for each group at all times. Changes within groups between baseline and week 12 and between groups for the clinical and laboratory parameters were analyzed using unpaired Student *t*-test, with a significance set up at $p < 0.05$. Results of the questionnaire were analyzed with the Wilcoxon rank test. Sample size calculation was based on the results obtained in a previous preliminary clinical study (changes and variation). The new calculation was made with a power of 95% and a risk alpha of 5%.

RESULTS AND DISCUSSION

This performed protocol studied the effect of Sinetrol-XPur on weight management; metabolic parameters; and inflammatory, glycemic, and oxidative status in overweight men and women. At the start of the study, there was no difference between groups with respect to age, BMI, height, body weight, and body fat (Table 1). Weight and waist and hip circumference continuously decreased during the study (data not shown). After 12 weeks of treatment, percent changes in waist and hip circumference, abdominal body fat, and body weight for the Sinetrol-XPur group were statistically lower than those of the placebo group (Table 2). Waist reduction was 5.71% for the Sinetrol-XPur group versus 1.56% for the placebo group ($p < 0.0001$), corresponding to a mean waist reduction of 5.15 versus 1.42 cm, respectively. Hip circumference decreased by 4.71% for Sinetrol-XPur compared with 1.35% for placebo, corresponding to a mean hip reduction of 5.17 and 1.43 cm respectively ($p < 0.001$).

The waist-to-hip ratio was 0.809 and 0.808 for the placebo group at baseline and W12, respectively, with the lowest level (0.784) found for the Sinetrol-XPur group after 12 weeks of treatment. The change (%) in this ratio was not significant between the two groups. A $9.73 \pm 0.54\%$ reduction of body fat was observed in the Sinetrol-XPur group, whereas only $3.18 \pm 0.33\%$ was lost by the placebo group, with a difference between the two groups being highly significant ($p < 0.0001$). Body weight decreased by $3.28 \pm 0.24\%$ for Sinetrol-XPur compared with $2.09 \pm 0.17\%$ for placebo ($p < 0.0001$), corresponding to a loss of 2.62 vs 1.6 kg, respectively.

Previously, a small clinical study versus placebo has evaluated the influence of a similar, yet not identical, citrus extract made of a variety of oranges and grapefruit plus guarana fruit on body weight and composition in 20 overweight and obese individuals for 12 weeks (Dallas *et al.*, 2008). Possible mechanisms of action included the result of citrus polyphenols on the inhibition of PDE, thereby prolonging the lipolytic-induced cAMP action. Another one may involve induction of the expression of fatty acid oxidation genes (Goldwasser *et al.*, 2010). This demonstrated that the combination of citrus fruits and guarana contains an array of potent bioactive compounds that can generate weight and fat loss.

A safety study showed that kidney function, liver enzymes, blood pressure, and serum lipid profile (except ApoA) were not statistically different at the beginning of the study and between Sinetrol-XPur and placebo groups after 12 weeks of treatment (Table 3). Heart rate did not change in the placebo group but was slightly higher in the Sinetrol-XPur group by the end of the study ($+3.32\%$), although all values remained within normal limits (74 to 77 rates/min). The increase in cardiac rate corresponds to what would be experienced after consuming three cups of coffee per day related to the content of caffeine (19.8 mg/day).

The FFA significantly increased in both groups (Table 3). However, the rise in the Sinetrol-XPur group ($+329.73 \pm 14.68\%$) was significantly greater than that for placebo ($+33.16 \pm 4.6\%$) ($p < 0.0001$). Lipolytic activity was clearly demonstrated by the high plasmatic change of FFA ($\approx 330\%$) probably related to the citrus polyphenol-inhibited PDE. The increase in plasma FFAs did not affect lipid profiles, which remained unchanged. Levels of cholesterol, TG, HDL, and LDL remained within normal limits. The HDL/LDL ratio

Table 1. Baseline characteristics of healthy overweight study sample by intervention group.

	Placebo	Sinetrol-XPur
<i>N</i>	48	47
Men, <i>n</i> (%)	20 (41.7)	20 (42.5)
Women, <i>n</i> (%)	28 (58.3)	27 (57.5)
Age (years)	37.8 ± 0.7	37.6 ± 0.7
Caucasian, <i>n</i> (%)	45 (93.7)	44 (93.6)
Others, <i>n</i> (%)	3 (6.3)	3 (6.4)
BMI (kg/m^2)	27.27 ± 0.14	27.58 ± 0.16
Body weight (kg)	77.39 ± 1.23	78.14 ± 1.35
Height (m)	1.69 ± 0.01	1.69 ± 0.01
Body fat (%)	36.87 ± 1.48	37.97 ± 1.59

Values are means \pm standard deviation or *n* (%). Groups did not differ at baseline.

Table 2. Percent change for BMI, weight, body fat, and waist and hip size at baseline and after 12 weeks of treatment with placebo or Sinetrol-XPur in healthy overweight adults

	Placebo			Sinetrol-XPur		
	Baseline	W12	% change	Baseline	W12	% change
BMI (kg/m ²)	27.27 ± 0.14	26.12 ± 0.35 ^a	-4.23 ± 1.12	27.58 ± 0.16	26.39 ± 0.33 ^a	-4.31 ± 1.02, NS
Body weight (kg)	77.39 ± 1.23	75.78 ± 1.23	-2.09 ± 0.17	78.14 ± 1.35	75.52 ± 1.25	-3.28 ± 0.24***
Body fat (%)	36.87 ± 1.48	35.85 ± 1.51	-3.18 ± 0.33	37.97 ± 1.59	34.36 ± 1.49	-9.73 ± 0.54***
Waist (cm)	88.44 ± 1.09	87.02 ± 1.02	-1.56 ± 0.20	88.68 ± 1.05	83.53 ± 0.87 ^a	-5.71 ± 0.35***
Hip (cm)	109.90 ± 0.96	108.47 ± 0.99	-1.35 ± 0.19	110.08 ± 1.21	104.91 ± 1.23 ^a	-4.71 ± 0.29***
Waist/hip	0.809 ± 0.113	0.808 ± 0.101	-0.23 ± 1.69	0.813 ± 0.113	0.784 ± 0.155	-1.01 ± 2.28, NS

Values are means ± standard deviation, *n* = 48 (placebo) or 47 (Sinetrol-XPur). Group mean did not differ at baseline.

NS, not significant; W12, week 12.

^aAn intragroup difference between baseline and W12 at *p* < 0.05. Intergroup percent change differences:

**p* < 0.05;

***p* < 0.01;

****p* < 0.0001.

Table 3. Percent changes on clinical safety values (kidney, liver, cardiac function, and lipid profile) at baseline and after 12 weeks of treatment with placebo or Sinetrol-XPur in healthy overweight adults

	Placebo			Sinetrol-XPur		
	Baseline	W12	% change	Baseline	W12	% change
Kidney function						
Na (mmol/L)	134 ± 1	133 ± 1	-0.45 ± 0.82	136 ± 1	134 ± 1 ^a	-1.53 ± 0.55, NS
K (mmol/L)	4.4 ± 0.1	3.9 ± 0.1 ^a	-10.86 ± 1.48	4.5 ± 0.1	4 ± 0.1 ^a	-9.43 ± 1.55, NS
Urea (mmol/L)	6.3 ± 0.2	7 ± 0.2 ^a	18.87 ± 5.27	6.5 ± 0.3	7.5 ± 0.87 ^a	28.93 ± 7.06, NS
Creatinine (μmol/L)	106 ± 2	116 ± 2	12.63 ± 3.60 ^a	108 ± 2	113 ± 2	6.57 ± 3.53, NS
Liver function						
ALT (IU/L)	26.17 ± 1.61	19.87 ± 0.53 ^a	-18.42 ± 3.25	25.49 ± 0.67	18.85 ± 0.48 ^a	-23.13 ± 3.40, NS
AST (IU/L)	26.40 ± 0.84	24.62 ± 0.43	-3.11 ± 3.34	26.60 ± 0.68	23.96 ± 0.49 ^a	-6.75 ± 3.66, NS
GGT (IU/L)	40.68 ± 1.51	35.58 ± 0.68 ^a	-5.86 ± 4.67	43.04 ± 1.38	34.43 ± 0.71 ^a	-16.35 ± 2.37, NS
CPK (IU/L)	142.34 ± 5.9	112.25 ± 3.69 ^a	-13.71 ± 4.64	156.83 ± 6.0	112.21 ± 2.91 ^a	-23.36 ± 3.60, NS
Cardiac function						
Heart rate (beats)	74.33 ± 0.74	74.64 ± 0.77	-0.51 ± 0.68	74.74 ± 0.90	77.06 ± 0.78	3.32 ± 0.76**
SBP (mmHg)	131.29 ± 1.1	131.90 ± 1.09	0.52 ± 0.46	133.91 ± 1.1	136.08 ± 1.2	1.67 ± 0.47, NS
DBP (mmHg)	74.04 ± 0.69	74.58 ± 0.63	0.97 ± 0.91	74.85 ± 0.68	77.11 ± 0.69	3.12 ± 0.68, NS
Lipids profile						
Chol (mmol/L)	5.96 ± 0.11	5.74 ± 0.74	-2.44 ± 2.05	6.02 ± 0.11	5.59 ± 0.06	-5.83 ± 1.90, NS
TG (mmol/L)	1.29 ± 0.06	1.38 ± 0.03	19.75 ± 6.40	1.33 ± 0.05	1.38 ± 0.03	12.42 ± 5.72, NS
HDL (mmol/L)	1.46 ± 0.04	1.40 ± 0.03	-0.83 ± 3.33	1.49 ± 0.04	1.49 ± 0.03	2.71 ± 3.32, NS
LDL (mmol/L)	3.67 ± 0.08	3.51 ± 0.06	-2.33 ± 2.30	3.61 ± 0.09	3.43 ± 0.05	-2.61 ± 2.37, NS
ApoA (μmol/L)	50.95 ± 1.18	46.75 ± 0.38	-5.89 ± 2.39	50.76 ± 1.21	51.85 ± 0.53	5.38 ± 3.02*
ApoB (μmol/L)	2.26 ± 0.07	2.75 ± 0.03	27.30 ± 4.78	2.21 ± 0.06	2.50 ± 0.03	17.65 ± 4.19, NS
FFA (μmol/L)	152.1 ± 4.05	197.93 ± 6.3 ^a	33.16 ± 4.6	151.15 ± 2.96	638.63 ± 17.11 ^a	329.73 ± 14.68***

Values are means ± standard deviation, *n* = 48 (placebo) or 47 (Sinetrol-XPur). Group mean did not differ at baseline.

ALT, alanine amino transaminase; Apo, apolipoprotein; AST, aspartate amino transaminase; Chol, cholesterol; CPK, creatinine phosphokinase; DBP, diastolic blood pressure; FFA, free fatty acid; GGT, gamma-glutamyl transpeptidase; HDL, high-density lipoprotein; IU, international units; LDL, low-density lipoprotein; NS, not significant; SBP, systolic blood pressure; TG, triglyceride; W12, week 12.

^aAn intragroup difference between baseline and W12 at *p* < 0.05. Intergroup percent change differences:

**p* < 0.05;

***p* < 0.01;

****p* < 0.0001.

was also within normal limits (between 0.39 and 0.43). A recent epidemiologic and experimental study (Green *et al.*, 1985) suggested that the HDL/LDL ratio may adequately represent the joint contribution of the lipoproteins to heart disease. Alone, ApoA increased in

the Sinetrol-XPur group by 5.38 ± 3.02% compared with a decrease of 5.89 ± 2.38% in the placebo group, with a statistically significant difference (*p* < 0.05). Previous studies have shown that citrus flavonoids such as naringenin are effective plasma lipid-lowering agents

on laboratory animals, especially those fed with a high-cholesterol diet (Gorinstein *et al.*, 2005; Mulvihill *et al.*, 2009). Both citrus flavonoids and palm tocotrienols or pomelo–grapefruit hybrid fruit juice reduce cholesterol levels in hypercholesterolemic patients (Gorinstein *et al.*, 2003; Roza *et al.*, 2007). We speculated that this lack of effect in our study suggests a different flavanone profile in Sinetrol-XPur than the ones used in the studies quoted earlier.

Another key link between increasing fat mass and obesity-related complications is a chronic low-grade inflammatory state and an increased oxidative stress. Previous studies have shown the direct link between a high level of inflammatory biomarkers (such as CRP and fibrinogen) and obesity-related diseases such as diabetes, hypertension, and CV diseases in overweight and obese people (de Ferranti and Mozaffarian, 2008; Nguyen *et al.*, 2009). In our study, at baseline, there was no difference between groups with respect to those parameters (Table 4). No subject displayed any sign of infection throughout the study (data not shown). Inflammatory markers (as expressed by CRP and fibrinogen) showed significant differences between the Sinetrol-XPur and placebo groups. CRP decreased by $22.87 \pm 7.30\%$ with Sinetrol-XPur, whereas they increased by $61.79 \pm 14.44\%$ with the placebo, and the difference between the two groups was highly significant ($p < 0.0001$). Fibrinogen levels decreased by $19.91 \pm 2.04\%$ with Sinetrol-XPur, whereas they remained the same for placebo. The difference between the two groups was significant ($p < 0.0001$).

The related effect of Sinetrol-XPur on oxidative status was evaluated by measuring plasma MDA, SOD, and GSH. At baseline, these levels were within normal range with no significant difference between groups. By the end of the study, MDA decreased by $14.03 \pm 1.18\%$ in the Sinetrol-XPur group compared with a slight increase in the placebo group ($2.76 \pm 1.61\%$) with a highly significant difference between the two groups ($p < 0.0001$). SOD increased in the Sinetrol-XPur group

eight times more than in the placebo group ($17.38 \pm 4.08\%$ vs $2.19 \pm 3.66\%$, $p < 0.01$). GSH levels increased by $4.63 \pm 11.62\%$ in the Sinetrol-XPur group, whereas they decreased by $2.36 \pm 1.13\%$ in placebo group ($p < 0.01$). We have shown that a 12-week consumption of a citrus polyphenolic dietary supplement had beneficial changes in measures related to inflammation status including a significant decrease of circulating levels of CRP ($\approx 23\%$) and fibrinogen ($\approx 20\%$). In our current study, supplementation with Sinetrol-XPur led to an improvement in oxidative status in overweight healthy subjects. After 12 weeks of treatment, Sinetrol-XPur significantly decreased MDA plasma levels (almost equal to -14%) and increased SOD and GSH levels ($\approx 17\%$ and $\approx 5\%$, respectively). Therefore, consumption of anti-inflammatory and antioxidant substances contained in fruits could be a useful strategy to add to weight loss programs to boost the benefits of losing fat and reducing risk factors and complications associated with excess weight (Crujeiras *et al.*, 2006).

Mean fasting blood sugar levels were normal at baseline in each group (Table 4). However, blood sugar further decreased by $9.95 \pm 1.87\%$ in the Sinetrol-XPur group, whereas it increased by $5.40 \pm 1.90\%$ in the placebo groups with a significant difference between the two groups ($p < 0.0001$). Concurrently, HbA1c rose slightly by $7.15 \pm 12.56\%$ in the Sinetrol-XPur group and by a higher level ($24.35 \pm 2.46\%$) in the placebo group, although all values remained within normal limits (less than 7%). This difference between fasting blood sugar and HbA1c can be explained by the fact that changes in HbA1c can only be observed after 3 months. We can expect a more relevant decrease of the HbA1c after a longer period of treatment with Sinetrol-XPur (6–9 months).

Grapefruit and grapefruit products that contain naringenin and naringin have been shown to reduce insulin resistance in subjects with metabolic syndrome (Fujioka *et al.*, 2006). An inhibition of intestinal glucose uptake and renal glucose reabsorption by naringenin can

Table 4. Percent changes for inflammatory, oxidative, and glycemc status at baseline and after 12 weeks of treatment with placebo or Sinetrol-XPur in healthy overweight adults.

	Placebo			Sinetrol-XPur		
	Baseline	W12	% change	Baseline	W12	% change
Inflammation						
CRP (nmol/L)	26.46 ± 2.09	34.75 ± 1.99^a	61.79 ± 14.44	33.12 ± 2.95	20.84 ± 1.9^a	$-22.87 \pm 7.30^{***}$
Fibrinogen ($\mu\text{mol/L}$)	10.26 ± 0.29	10.14 ± 0.20	-1.61 ± 2.59	10.81 ± 0.29	8.77 ± 0.14^a	$-19.93 \pm 2.04^{***}$
Oxidative status						
MDA ($\mu\text{mol/l}$)	2.99 ± 0.5	3.04 ± 0.5	2.76 ± 1.61	2.94 ± 0.06	2.52 ± 0.05^a	$-14.03 \pm 1.18^{***}$
SOD (IU/Hb)	1339.7 ± 40.6	1330.1 ± 35.7	2.19 ± 3.66	1276.6 ± 37.9	1436.7 ± 33.9^a	$17.38 \pm 4.08^{**}$
GSH ($\mu\text{mol/l}$)	878.65 ± 7.91	854.08 ± 4.24	-2.36 ± 1.13^a	868.92 ± 10.20	898.66 ± 5.93^a	$4.63 \pm 1.62^{**}$
Glycemc status						
Glycemia (mmol/L)	5.7 ± 0.1	5.9 ± 0.1^a	5.40 ± 1.90	5.8 ± 0.1	5.2 ± 0.1^a	$-9.95 \pm 1.87^{***}$
HbA1c (%)	5.55 ± 0.10	6.79 ± 0.05^a	24.32 ± 2.46	5.64 ± 0.10	5.95 ± 0.08^a	$7.15 \pm 2.56^{***}$

Values are means \pm standard deviation, $n = 48$ (placebo) or 47 (Sinetrol-XPur). Group mean did not differ at baseline.

CRP, C-reactive protein; Hb, hemoglobin; IU, international units; GSH, glutathione; MDA, malondialdehyde; NS, not significant; SOD, superoxide dismutase; W12, week 12.

^aAn intragroup difference between baseline and W12 at $p < 0.05$. Intergroup percent change differences:

* $p < 0.05$;

** $p < 0.01$;

*** $p < 0.0001$, NS = not significant.

explain, at least partially, the *in vivo* antihyperglycemic action of naringenin and its derivatives. Naringenin also improves insulin sensitivity and glucose metabolism in metabolic syndrome-prone mice (Mulvihill *et al.*, 2009).

In conclusion, the safety of Sinetrol-XPur supplementation was assessed in our study during 12 weeks on kidney and liver parameters. Sinetrol-XPur had no effect on blood pressure. We suggest that consumption of Sinetrol-XPur produces beneficial changes in body fat composition and improves inflammatory, glycemic, and oxidative status in overweight healthy individuals.

When taken twice a day for 12 weeks, Sinetrol-XPur supplement was well tolerated with no adverse effects. However, additional research is warranted to delve deeper into the mechanisms of action and confirm these results over a longer period.

Conflict of Interest

The corresponding author and all the authors have read and approved the final submitted manuscript. The authors declare no conflict of interest.

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