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Effects of *Citrus aurantium* Extract, Caffeine, and St. John's Wort on Body Fat Loss, Lipid Levels, and Mood States in Overweight Healthy Adults

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ABSTRACT

The purpose of this study was to determine the effects of *Citrus aurantium* extract (an indirect beta-sympathomimetic agent), caffeine, and St. John's Wort on body composition, metabolic variables, plasma lipid levels, and mood states in overweight healthy adults. In a double-masked, randomized, placebo-controlled study, 23 subjects with a body-mass index $>25 \text{ kg/m}^2$ were assigned to 1 of 3 groups. Group A received *C. aurantium* extract 975 mg, caffeine 528 mg, and St. John's Wort 900 mg daily; group B received a maltodextrin placebo; and group C received nothing and served as the control group. For 6 weeks, subjects were instructed by a registered dietitian on how to follow an 1800-kcal/d American Heart Association Step One diet and performed a 3-day/week circuit training exercise program under the supervision of an exercise physiologist. During the exercise sessions, subjects achieved approximately 70% of age-predicted maximum heart rate. Compared with subjects in the placebo and control groups, subjects in the treatment group lost a significant amount of body weight (1.4 kg). They also lost a significant amount of body fat (an average change of 2.9%). In terms of actual fat loss, group A lost a significant amount (3.1 kg), whereas the control group demonstrated a tendency toward fat loss. No significant changes were noted in the results of the Profile of Mood States questionnaire for fatigue or vigor in any of the 3 groups. Group A experienced a decrease, which did not reach statistical significance, of both plasma cholesterol and triglycerides. No significant changes in blood pressure, heart rate, electrocardiographic findings, serum chemistries, or urinalysis findings were noted in any of the groups. Based on these results, it was concluded that the combination of *C. aurantium* extract, caffeine, and St. John's Wort is safe and effective when combined with mild caloric restriction and exercise for promoting both body weight and fat loss in healthy overweight adults. *Key words:* *Citrus aurantium*, caffeine, St. John's Wort, synephrine, weight loss, obesity, exercise, nutrition.

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INTRODUCTION

One or more of the following factors are postulated to contribute to the development of obesity: familial genetics, lack of physical activity, over-consumption of foods, or physiologic conditions.¹⁻³ Currently, obesity has reached epidemic proportions in the United States. The prevalence of obesity has increased from 25% to 33% over the 10 years between the second and most current National Health and Nutrition Examination Survey.⁴ The health risks associated with obesity include type 2 diabetes mellitus; hypertension; coronary artery disease; hyperlipidemia; stroke; endometrial, postmenopausal breast, and colon cancer; sleep apnea; gallbladder disease; gastroesophageal reflux disease; fatty liver; osteoarthritis; gout; infertility; and thromboembolism.⁴ Some components of a comprehensive weight loss program include medical assessment; modifications in behavior, diet, and exercise; and long-term follow up.

In an attempt to lose weight, obese individuals often restrict calories, with a resulting adaptive decrease in energy expenditure. This decrease in energy expenditure is directly correlated to a reduction in the functional state of the sympathetic nervous system (SNS).⁵ The SNS may be subject to defects, thereby predisposing individuals to weight gain.⁶ Physiologically, reduced SNS functioning translates into reduced adrenaline-induced (norepinephrine and epinephrine) thermogenesis.⁵ Norepinephrine and epinephrine physiologically affect many systems. One such known effect is on metabolism, specifically of carbohydrates, lipids, and protein.

It has been observed that genetically obese rats exhibit low sympathetic outflow or responsiveness in various tissues.⁷ The beta-adrenergic receptors are involved in the pathways of lipolysis, glycogenolysis, and thermogenesis; lipolysis and thermogenesis are mediated via the beta-3 receptor.^{8,9} Indirect-acting sympathicomimetic compounds potentiate the release of epinephrine and norepinephrine at presynaptic sites in the SNS. Studies with indirect sympathicomimetic drugs, such as ephedrine in humans, have been successful as potential slimming agents; these studies often use a methylxanthine, such as caffeine or theophylline, to potentiate thermogenesis.^{10,11} Despite actions facilitating fat loss, stimulatory agents or combinations thereof using ephedrine may induce negative side effects in some individuals (nervousness, tachycardia, hypertension, dry mouth).^{5,10} Another indirect sympathicomimetic agent is synephrine, which is isolated from *Citrus aurantium*. Although, like ephedrine, this substrate is adrenergic, it is synephrine based (alkaloids) and thus may offer a wider margin of safety. Depressive symptoms have also been correlated to weight gain and the amplification of age-associated weight change. St. John's Wort has been investigated as a treatment for some types of mild-to-moderate depression.¹²⁻¹⁴

The objective of the present study was to assess the utility of the combination of *C aurantium* extract, caffeine, and St. John's Wort plus a diet and an exercise plan for fat loss in healthy overweight adults.

SUBJECTS AND METHODS

Using a double-masked, randomized, placebo-controlled protocol, subjects were assigned to 1 of 3 groups: group A, treatment; group B, placebo; or group C, control. Healthy adults (older than 21 years of age) with a body-mass index greater than 25 kg/m² were eligible to participate in the study. Written informed consent was obtained from all of the subjects in accordance with the American College of Sports Medicine's policy regarding human research. Exclusion criteria included history of thyroid or heart disease, cancer, human immunodeficiency virus or acquired immunodeficiency syndrome, pregnancy, lactation, hypertension, use of monoamine oxidase inhibitors, and current use of a restricted-calorie diet or anorectic medication. Subjects were also excluded if they had no history of exercise or physical activity. Consumption of alcohol was prohibited during the investigation.

Subjects in group A received a compound containing *C aurantium* extract (6% synephrine alkaloid) 975 mg, caffeine 528 mg, and St. John's Wort (3% hypericum) 900 mg (Twin Laboratories, Inc., Hauppauge, New York); group B received a maltodextrin placebo; and group C received nothing and served as the control group. All capsules looked and tasted the same. To best ensure pill compliance, subjects returned any unused pills at their scheduled laboratory visit. Each subject was evaluated at baseline, week 3, and week 6. All appointments were with the same technical personnel at approximately the same time of day. Total body weight was measured using a Detecto™ balanced medical scale (Detecto Scale, Webb City, Missouri) at each laboratory visit. Subjects were weighed after a 4-hour fast and voiding of the bladder, and each subject was weighed wearing only essential clothing. After 4 hours of fasting, body composition was determined by means of bioelectrical impedance analysis (Model 3.10, Biodynamics, Seattle, Washington).

All subjects engaged in a 3-day/week circuit training exercise program. The program was performed under the guidance of an exercise physiologist for 45 minutes per session. Subjects achieved approximately 70% of age-predicted maximum heart rate (Karvonen formula) and approximately 70% of predicted 1 repetition maximum (ie, bench press). Sessions were a combination of step aerobics and weight training. Each subject received individual instruction by a registered dietitian about the 1800-kcal/d American Heart Association Step One diet. They were also given 1800-kcal/d meal plans, daily menus, and restaurant guidelines. Furthermore, to best ensure dietary compliance, each subject received

weekly follow-up telephone calls and biweekly dietary review sessions with the registered dietitian. Multiple 24-hour dietary recalls were also taken at laboratory visits. To determine whether treatment had any influence on feelings of vigor or fatigue, a Profile of Mood States (POMS) questionnaire (Educational and Industrial Testing Service, San Diego, California) was used.

Biochemical data (serum chemistries, complete blood cell count [CBC] with differential, total cholesterol, and triglycerides) were measured at each scheduled laboratory visit. Blood was drawn from the antecubital vein and processed by Quest Diagnostics (Wallingford, Connecticut). Each subject also underwent multiple electrocardiographic procedures (Burdick Eclipse 800, Deerfield, Wisconsin), which were administered at baseline, week 3, and week 6. In addition, urinalysis (Chemstrip Analyzer, Indianapolis, Indiana) was performed for all subjects to assess any effect on urinary glucose or protein, and specific gravity was determined as an indication of concentrated urine and dehydration.

Any abnormal or significant changes within any of the variables tested as well as verbal reports by the subjects were deemed adverse events.

Statistical Analysis

Each group was tested for intergroup and intragroup variances. Paired t tests were used for within-group changes over time, and analysis of variance was used to test for time/group interactions to compare changes over time among groups. Significance was set at $P < 0.05$.

RESULTS

Twenty-three subjects entered the study; 20 completed the entire 6 weeks. Three individuals dropped out for reasons unrelated to the study. No significant differences in characteristics were noted at baseline among the 3 study groups: group A ($n = 9$), group B ($n = 7$), and group C ($n = 4$) (Table I). The 3 groups were similar in age, systolic and diastolic blood pressures, POMS scores, body-mass index, body weight, percent body fat, kilograms of actual fat, lean body mass, basal metabolic rate, serum glucose, total cholesterol, and triglycerides.

Over the 6-week period, subjects in group A lost a significant amount of body weight (1.4 kg, $P < 0.05$) compared with subjects in the placebo and control groups. In addition to losing body weight, group A subjects also achieved a significant reduction in body fat, with an average change of 2.9% (26.3% pretreatment to 23.4% post treatment; $P < 0.05$). The placebo group did show a trend in percent body fat lost and in total body weight lost ($P = 0.10$ and $P = 0.10$, respectively). However, neither the placebo group nor the control group lost a significant amount of body fat ($P > 0.10$).

Table I. Baseline characteristics. Unless otherwise noted, values are given as mean \pm SD.

Measure	Group A (n=9)	Group B (n=7)	Group C (n=4)	<i>P</i> *
Age (y)	38.0 \pm 15	41.1 \pm 9.1	57.8 \pm 8.9	0.51
Body-mass index (kg/m ²)	29.5 \pm 2.8	28.8 \pm 3.4	26.8 \pm 1.7	0.34
Body weight (kg)	90.9 \pm 17.5	83.6 \pm 17.5	78.1 \pm 11.5	0.19
Percent body fat	26.3 \pm 7.1	25.4 \pm 5.6	23.2 \pm 4.6	0.72
Fat mass (kg)	24.6 \pm 11.3	20.8 \pm 6.05	17.8 \pm 2.6	0.17
Basal metabolic rate (kcal/d)	2026 \pm 279	1908 \pm 456	1859 \pm 304	0.73
Serum glucose (mg/dL)†	89 \pm 18.2	86.1 \pm 18.2	88 \pm 17.9	0.77
Total cholesterol (mg/dL)†	216 \pm 62	200 \pm 45	209 \pm 50	0.60
Triglycerides (mg/dL)†	119 \pm 65	169 \pm 153	142 \pm 88	0.47

Group A = treatment (*Citrus aurantium* extract, caffeine, and St. John's Wort); group B = maltodextrin placebo; group C = control. *Analysis of variances used for the group comparisons. †Fasting values.

In terms of actual fat loss, the treatment group lost 3.1kg ($P=0.01$), whereas the placebo group did not lose any significant fat weight. The control group demonstrated a tendency toward fat loss. In addition, subjects in group A realized a significant increase in their basal metabolic rate, from 2026 to 2069 kcal/d ($P < 0.05$) (Table II)

Table II. Physical and metabolic changes. Unless otherwise noted, values are given as mean \pm SD

Measure	Baseline	Week 6	Percent change	<i>P</i> *
Body weight (kg)				
Group A	90.9 \pm 17.5	89.5 \pm 16	-1.5	0.05
Group B	83.6 \pm 17.5	82.7 \pm 18	-1.1	0.10
Group C	78.1 \pm 11.5	77.7 \pm 10.5	-0.05	NS
Percent body fat				
Group A	26.3 \pm 7.1	23.4 \pm 6.9	-2.9†	0.01
Group B	25.4 \pm 5.6	26.2 \pm 4.8	+1.8	NS
Group C	23.2 \pm 4.6	21.0 \pm 3.7	-2.2	0.10
Fat mass (kg)				
Group A	24.6 \pm 11.3	21.5 \pm 10.1	-13.0†	0.01
Group B	20.8 \pm 6.05	21.5 \pm 5.9	+0.3	NS
Group C	17.8 \pm 2.6	16.0 \pm 1.4	-10.0	0.10
Basal metabolic rate (kcal/d)				
Group A	2026 \pm 279	2069 \pm 268	+3.0†	0.05
Group B	1908 \pm 456	1868 \pm 437	-3.0	0.05
Group C	1859 \pm 304	1870 \pm 300	+0.1	0.10

Group A (n=9) = treatment (*Citrus aurantium* extract, caffeine, and St. John's Wort); group B (n=7) = maltodextrin placebo; group C (n=4) = control. *Paired *t* tests were used for change over time. Repeated measures of analysis of variance were used to test time/group interactions to compare change over time among groups. † $P < 0.05$ versus groups B and C.

Biochemically, no insult or significant changes were evident according to liver function test results (aspartate aminotransferase, alanine amino-transferase, gamma-glutamyltransferase), renal function (blood urea nitrogen, serum creatinine), or bone marrow function (CBC with differential and platelets). All laboratory test results remained within normal limits. The electrocardiograms did not show any changes over time nor did the urinalysis indicate any incidence of glycosuria, proteinuria, or excessive concentration. No significant changes in serum glucose were noted in any of the groups. Both total cholesterol and serum triglycerides showed a tendency to decrease in the treatment group ($P = 0.10$ and $P = 0.10$, respectively), whereas no significant changes were noted in either the placebo or control groups.

DISCUSSION

In an attempt to lose weight, obese individuals commonly restrict calories. The result is an adaptive response of a lowered basal metabolic rate along with accompanying loss of skeletal muscle. Weight loss or reducing caloric intake results in a compensatory response of lowering resting energy expenditure.¹⁵ As noted by Daly et al.,⁵ reduced functionality of the SNS is apparent with caloric restriction and may be one cause of decreased energy expenditure. In the present study, lowered resting energy expenditure was avoided by preventing the decline in metabolic rate associated with a reduced-calorie diet, primarily by stimulating lipolysis and enhancing basal metabolism.¹⁶ Sympathomimetic agents are known to facilitate weight loss, as described previously.^{5,6,11} Basal metabolic rate was significantly elevated in subjects receiving synephrine alkaloids. This is a finding consistent with other studies^{17,18} using sympathomimetic agents.

Synephrine alkaloids are mild, indirect-acting, mixed adrenergic agents that exert their effects by means of liberation of epinephrine and dopamine from the presynaptic terminal. When compared with ephedrine, synephrine alkaloids do not exactly replicate the effects of ephedrine; less central nervous system stimulation was evident with *C aurantium* extract in the dosages used in this investigation (personal communication, Dr. Rejeanne Gougeon, McGill University, Royal Victoria Hospital, Quebec, Canada, February 10, 1998).

Pharmacokinetic data indicate synephrine alkaloids are less lipophilic than ephedrine and hence do not readily cross the blood-brain barrier.¹⁹ The unique metabolism of *C aurantium*, may predispose this compound for thermogenic effects, while keeping side effects at a minimum (R. Gougeon, MD, unpublished data, 1998). Past investigations of ephedrine, caffeine, and aspirin have shown negative effects, especially at the onset of treatment.

The most commonly reported side effects are palpitations, tremor, increase in blood pressure, dry mouth, and insomnia.⁵ These negative reactions did not occur with subjects in the present study.

Subjects receiving treatment (group A) showed a significant decrease in both body weight and body fat, whereas the placebo and control groups showed little or no changes in fat mass. Despite stimulation of the SNS, no side effects were reported. This may be due in part to the mechanism of action of *C aurantium* extracts when mixed with a methylxanthine. On the cellular level, synephrine (an alkaloid found within *C aurantium*) enhances the release of norepinephrine from the sympathetic nerve terminal. As the level of released norepinephrine increases, adenosine and prostaglandins are synthesized by the stimulated tissue and act as prejunctional inhibitors. The thermogenic response may be limited by activation of cyclic adenosine monophosphate (cAMP) or intracellular feedback inhibition by phosphodiesterase enzymes. Octopamine (another alkaloid found within *C aurantium*) reportedly couples with the alpha-2A adrenoreceptors in a dose-dependent manner, yielding a decrease in cAMP production.²⁰ Thus methylxanthines, by antagonizing adenosine and phosphodiesterases, reduce or remove these prejunctional and intracellular inhibitors, thereby increasing and sustaining activation of the effector cell by norepinephrine.⁵

Laboratory testing (including vital signs, serum chemistries, CBC with differential, urinalysis, and electrocardiography) revealed no significant changes. This indicates that the compounds from the *C aurantium*, caffeine, and St. John's Wort combination caused no measurable abnormal physiologic consequences. As with other thermogenic agents studied previously,^{5,9,16,17} the combination of *C aurantium* extract, caffeine, and St. John's Wort appears to be well tolerated.

Of interest to those treating obese patients is the mental status of these individuals. It has been noted that depression may be a causative or reactive factor in the etiology of obesity.²¹ For this reason, pharmacologic intervention might be warranted. Symptoms of depression have been correlated to weight gain.¹² St. John's Wort is considered to be a safe antidepressant with efficacy in the treatment of patients with mild-to-moderate depression.^{13,22} It is a potent uptake inhibitor of serotonin (5-hydroxytryptophan), dopamine, noradrenaline, gamma-aminobutyric acid, and L-glutamate.²² The effects of this herb apparently are translated into reduced feelings of despair, enhanced feelings of well-being, and reduced scores of depression on the Hamilton Rating Scale for Depression.²³ Thus St. John's Wort may be an effective agent, in the treatment of mild-to-moderate depression in the presence of obesity. Future research with St. John's Wort perhaps should focus only on the treatment of patients with mild-to-moderate depression.

CONCLUSIONS

C aurantium extract is a noncentrally acting, beta-sympathomimetic agent, which, when combined with caffeine and St. John's Wort—as well as caloric restriction and exercise—can induce weight loss to a greater extent than diet and exercise alone. This investigation shows that a combination of *C aurantium extract*, caffeine, and St. John's Wort is viable and effective in reducing body fat in obese healthy adults.

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