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SYNEPHRINE AND *C. AURANTIUM* EXTRACT IN FOOD SUPPLEMENTS: ANALYSIS OF SAFETY AND HEALTH CLAIMS

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Summary. Obesity is a major health problem facing both the developed and developing world. Food supplements are promising support in programs for weight control. A large number of food supplements containing sympathomimetic such as synephrine, octopamine and *Citrus aurantium* are used for weight loss. The aim of this work is to analyse claims of food supplements containing synephrine and *C. aurantium* extract, available on the Bulgarian market and to compare them with the results of the published studies of safety and health effects of the substances. It also aims to evaluate the risk for the consumers. Literature search of publication for safety and health effects of both products were performed and results were compared with the information in the product leaflets. A pharmacoepidemiology evaluation of the severity and outcomes of the reported adverse events was performed. Out of the 15 selected studies only 3 reported positive efficacy events. Although some evidences regarding the efficacy of these substances are promising, there is a need of more investigations in order to support the claims. On the other hand, out all 15 studies 12 reported adverse events. 3 of the adverse events were evaluated as very serious, 2 as serious and 3 were deadly. There is a need for tight control by the relevant authorities for justification of product claims. It is very necessary that physicians and pharmacists obtain up-to-date information in order to justify the claims and safety of food supplements for weight loss.

Key words: food supplements, synephrine, *C. aurantium* extract, claims

SYNEPHRINE И *C. AURANTIUM* ЕКСТРАКТ В ХРАНИТЕЛНИ ДОБАВКИ – ОЦЕНКА НА ТВЪРДЕНИЯТА ЗА ЕФЕКТ И БЕЗОПАСНОСТ

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Резюме. Наднорменото тегло е световен здравен проблем както за развитите, така и за развиващите се страни. Значителен брой хранителни добавки, съдържащи симпатикомиметици като синефрин, октопамин и екстракт от *Citrus aurantium*, се предлагат за редукция на теглото. Цел на настоящата работа е да анализира здравните претенции на хранителните добавки, съдържащи synephrine и *C. aurantium* extract, които се разпространяват на българския пазар, и да ги сравни с резултатите от публикувани проучвания за ефекта и безопасността на двете субстанции. Проведено е проучване на публикации за здравните ефекти и безопасността на двата продукта, което е сравнено с информацията от листовките към хранителните добавки, които ги съдържат. Фармакоепидемиологично са оценени тежестта и изходът от докладваните нежелани реакции. От 15 селектирани проучвания само 3 докладват положителни резултати от ефекта на продуктите. Въпреки наличните данни за възможен ефект са необходими повече проучвания, за да бъдат подкрепени. От друга страна, 12 от проучванията докладват нежелани ефекти, от които 3 са оценени като много сериозни, 2 като сериозни и 3 като смъртоносни при над 1% от употребяващите. Необходим е контрол от страна на заинтересованите институции относно преценката на здравните претенции на хранителните добавки. Лекарите и фармацевтите следва да разполагат с актуална информация, която да им даде възможност да оценят адекватно претенциите и безопасността на хранителните добавки за редукция на теглото.

Ключови думи: хранителни добавки, синефрин, *C. aurantium* екстракт, здравни претенции

Introduction

Obesity is a major health problem facing both the developed and developing world [16]. Food supplements are promising support in programs for weight control. A large number of substances with various structure, origin and physiological properties are included in food supplements for weight reduction as they decrease the energy intake and energy absorption, and/or increase the metabolic rate. Significant part of those products include sympathomimetics such as synephrine, octopamine, or *Citrus aurantium* extract (*C. aurantium* L. Family: Rutaceae, bitter orange) which contains both substances [2, 20, 21, 22, 25, 29]. In April 2004, The US Food and Drug Administration (FDA) prohibited the sale of food supplements containing ephedrine in the US due to reports of adverse effects such as increased blood pressure, arrhythmia, tachycardia, myocardial infarction, stroke, hemorrhage, sudden death, seizures and psychiatric symptoms [11, 13]. After the ban on the sale of ephedra-containing products by FDA, "ephedra-free" food supplements containing synephrine and *C. aurantium* extract became very popular for weight loss. As these substances are structurally similar to ephedrine, their safety and efficacy need to be well documented with clinical and/or epidemiological trials [3, 5, 6, 9, 12, 23].

The aim of this work is to analyse claims of food supplements containing synephrine and *C. aurantium* extract, available on the Bulgarian market and to compare them with the results of the published studies of safety and health effects of the substances. It also aims to evaluate the risk for the consumers.

Materials and Methods

Safety and efficacy data analysis

The literature data bases Scopus, Dietary Supplements database of the US National Institutes of Health, and the World Anti-Doping Agency (WADA) were searched. A total of 15 publications on efficacy and safety of synephrine and *C. aurantium* extract published in the period 1999-2010 were selected. The publications were systematized according to the design of investigation and reported health effects and safety data.

Product claims analysis

The manufacturer's brochures and promotional materials of 27 food supplements, containing synephrine and *C. aurantium* extract, available on the Bulgarian market were analyzed for the included health effects and safety information.

A ***comparative analysis*** was performed of published health claims and safety data in both resources for evaluation of their conformity and accuracy.

Pharmacoepidemiology analysis

The reported adverse events in the published studies and information leaflets were evaluated for their seriousness and outcomes of adverse reactions by using the WHO CIOMS working group IV and Benicou scale [17].

Results and Discussion

Synephrine is not prohibited by Bulgarian relevant regulation [1], but it is included into the Monitoring Program of WADA. Octopamine is not prohibited either, but is present in the current WADA Prohibited List of World Anti-doping Code [30].

Systematization of the Synephrine and C. aurantium efficacy data in published studies

We have found the trials associated with the efficacy of synephrine and/or *C. aurantium* extract as presented on Table 1.

Colker et al. (1999) determined the effects of *C. aurantium* extract, 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 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 dietician 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), as well as 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. 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 urinanalysis findings were noted in any of the groups. Based on these results, the researches 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 [10].

Kalman et al. (2000) evaluated the safety of and efficacy of the ephedrine – and synephrine – based compound used for weight reduction. In their study, 30 subjects with a body mass index > 27 were assigned randomly to the experimental group or the placebo group. The experimental group received ephedrine alkaloids 20 mg, synephrine 5 mg, caffeine 200 mg, and salicin 15 mg twice daily for 8 weeks, whereas the other group received placebo. This regimen was complemented with dietician instructions and a cross-training exercise. The experimental group had a significantly greater weight loss compared with the placebo group (3.14 kg vs 2.05 kg, respectively; $P < 0.05$) and experienced a 16% decrease in body fat compared with a 1% increase for the placebo group. The between – group difference was significant ($P = 0.005$). No significant changes in blood pressure, serial electrocardiograms, pulse rate, serum chemistry, or caloric intake were noted [25].

Bent et al. (2004) performed a systematic review to examine the safety and efficacy of C. aurantium, based on an extensive search of MEDLINE, EMBASE, BIOSIS, and the Cochrane Collaboration Database. The search performed by the authors identified only 1 eligible randomized placebo controlled trial, which followed 20 patients for 6 weeks, demonstrated no statistically significant benefit for weight loss, and provided limited information about the safety of the herb [3].

Another minireview performed by Fugh-Berman et al. in 2004 found that there was a little evidence that products containing *C. aurantium* are an effective aid to weight loss. Synephrine, according to this review has lipolytic effects in human fat cells only at high doses, and octopamine does not have lipolytic effects in human adipocytes [15].

Gougeon et al. (2005) compared the thermo response to a meal between men and women to determine whether adrenergic amines extracted from *C. aurantium* induce an increase in metabolic rate and enhance the thermo response to the meal. The study was performed in 30 healthy weight-stable subjects (17 women, 13 men; BMI: 20 to 42 kg/m^2), body composition was determined by bio impedance analysis followed by resting energy expenditure for 20 minutes, and the thermo effect of food (TEF) of a 1.7-MJ, 30-gram protein meal was determined intermittently for 300 minutes by indirect calorimetric assessment. TEF was significantly lower in women than men (152 ± 7 vs. 190 ± 12 kJ and $8.8 \pm 0.4\%$ vs. $11.0 \pm 0.7\%$ of meal), independently of age and magnitude of adiposity. The thermic response to *C. aurantium* alone was higher in men, but, when added to the meal, *C. aurantium* increased TEF only in women and to values no different from men. *C. aurantium* had no effect on blood pressure and pulse rate but increased epinephrine excretion by 2.4-fold. A 20% lower TEF in women suggested a diminished sympathetic nervous system response to meals, because with *C. aurantium*, TEF increased by 29% only in women. However, the authors consider that this acute response may not translate into a chronic effect or a clinically significant weight loss over time [18].

Haaz et al. review (2006) concluded that while some evidence for efficacy of *C. aurantium* and synephrine is promising, larger and more rigorous clinical trials are necessary to draw adequate conclusions regarding the safety and efficacy for promoting weight loss [19].

In summary out of all 15 trials 3 reported positive efficacy events and all other were inconclusive. Thus we can not conclude that the health effects of both products could be considered proven.

Systematization of Synephrine and C. aurantium associated adverse events in published studies

The results presented on Table 1 provide the following information. Some studies suggest that sour orange juice is safe for normotensive subjects but individuals with severe hypertension, tachyarrhythmias, and narrow-angle glaucoma and monoamine oxidase inhibitor recipients should avoid it [19].

Three publications reported adverse events possibly associated with the use of bitter orange supplement such as acute lateral-wall myocardial infarction [27], arrhythmia [14] and variant angina [16].

Jordan et al. (2004) reported that from Jan. 1, 1998, to Feb. 28, 2004, Health Canada received 16 reports in which products containing bitter orange or synephrine were suspected of being associated with cardiovascular adverse events, including tachycardia, cardiac arrest, ventricular fibrillation, transient collapse and blackout. All cases were considered serious.

Bouchard et al. (2005) described a 38-year-old patient with ischemic stroke associated with an ephedra-free dietary supplement containing synephrine and caffeine. The patient presented with memory loss and unsteady gait after taking 1 or 2 capsules per day of a dietary supplement (Stacker 2 Ephedra-Free) for 1 week. Synephrine may be associated with ischemic stroke [4].

Table1. *Published studies focusing on health effects and safety characteristics of synephrine and C. aurantium extract*

Publication	**Type of publication**	**Health effects results**	**Safety results**
Colker et al. (1999) [10]	Double-masked, randomized, placebo-controlled study	***Positive result*** for the combination of *C. aurantium* extract, caffeine, and St. John's Wort when combined with mild caloric restriction and exercise	***Positive result*** for the combination of *C. aurantium* extract, caffeine, and St. John's Wort
Kalman et al. (2000) [25]	Placebo-controlled study	Positive result for the combination of ephedrine alkaloids 20 mg, synephrine 5 mg, caffeine 200 mg, and salicin 15 mg significantly greater weight loss in the experimental group compared with the placebo group (3.14 kg vs 2.05 kg) and 16% decrease in body fat compared with a 1% increase for the placebo group	***Positive result***: no significant changes in blood pressure, serial electrocardiograms, pulse rate, serum chemistry, or caloric intake were noted
Bent et al. (2004) [3]	Systematic review	Only 1 eligible randomized placebo controlled trial identified. No statistically significant benefit for weight loss	Limited information about the safety of the herb is provided.
Jordan et al. (2004) [24]	Review	N.A.	16 reports for serious cardiovascular adverse events
Fugh-Berman et al. (2004) [15]	Mini review	Little evidence that products containing *C. aurantium* are an effective aid to weight loss	N.A.
Gougeon et al. (2005) [18]	No placebo or control group	TEF increased by 29% only in women due to *C. aurantium* but the conclusion is that this acute response may not translate into a chronic effect or a clinically significant weight loss	Positive result: No effect on blood pressure and pulse rate
Min et al. (2005) [26]	Randomized, double-blind, placebo-controlled, crossover study	N.A.	No significant impact on QTc interval or blood pressure
Bouchard et al. (2005) [4]	Case study	N.A.	Ischemic stroke.
Haaz et al. review (2006) [19]	Review	Some evidences for efficacy of *C. aurantium* and synephrine are promising, but larger and more rigorous clinical trials are needed	Not safe for individuals with severe hypertension, tachyarrhythmias, and narrow-angle glaucoma and monoamine oxidase inhibitor recipients
Bui et al. (2006) [7]	Prospective, randomized, double-blind, placebo-controlled, crossover study	N.A.	Systolic blood pressure, diastolic blood pressure and heart rate were higher for up to 5 hours after a single dose of bitter orange versus placebo
Nykamp et al. (2004) [27], Firenzuoli F et al. (2005) [14]; Gange CA et al. (2006) [16]	3 case studies	N.A.	Lateral-wall myocardial infarction, arrythmia and variant angina
Burke J (2007) [8]	Case study	N.A.	Severe rhabdomyolysis
Stephensen et al. (2009) [28]	Case study	N.A.	Ventricular fibrillation

A randomized, double-blind, placebo-controlled, crossover study performed in 2005 in the University of Connecticut evaluated the hemodynamic and electrocardiographic effects of a single dose of commercially available bitter-orange dried-fruit extract [26]. Subjects were given either placebo or bitter-orange dried-fruit extract (450 mg standardized to 27 mg of m- or p-synephrine) in phase 1. The opposite treatment was given during phase 2 after a washout period of at least 7 days. The authors found that a single dose extract did not significantly alter the QTc interval or blood pressure and recommend future studies to ensure the multiple doses safety.

Bui et al. (2006) found in a prospective, randomized, double-blind, placebo-controlled, crossover study performed in 15 young, healthy, adult subjects, who received either a single dose of 900 mg dietary supplement of bitter orange extract (standardized to 6% synephrine) that systolic blood pressure, diastolic blood pressure and heart rate were higher for up to 5 hours after a single dose of bitter orange versus placebo [7].

One publication reported development of rhabdomyolysis after ingestion of a synephrine-containing dietary supplement. The patient developed fatigue, dehydration, and myalgia while exercising. The 22-year old male developed severe rhabdomyolysis, with a peak creatine phosphokinase level of 2.8 million U/L, complicated by pulmonary edema, acute renal failure, disseminated intravascular coagulation and bilateral compartment syndromes in his lower extremities. The patient required prolonged hospitalization for hemodialysis, multiple wound debridements, hyperbaric oxygen therapy, and physical therapy [8].

Stephensen et al. (2009) reported the case of a 27-year-old active duty female, military personnel in US who experienced an episode of ventricular fibrillation associated with the use of a dietary supplement containing synephrine [28].

In summary out of all 15 trials 2 reported positive effects, 1 was inconclusive, and all others reported adverse events.

Health and efficacy claims in leaflets and informational sources of the considered food supplements on the Bulgarian market

The analysis of 27 studied food supplement leaflets and manufacturers' materials revealed that all products contain 5 main claims:

– the products promote weight loss;
– the product burns fat;
– the product increase energy;
– the product increase metabolism and
– the product increase body heat.

No claims of possible adverse effects or safety reasons when applying the concrete supplement were found published in the reviewed leaflets.

Pharmacoepidemiology analysis

To evaluate the risk for the consumers we assess the seriousness and outcomes of the reported in clinical trials adverse events (Table 2). Three of them belong to the very serious and 2 to serious events according to the CIOMS IV scale. Three of the reported outcomes are connected with the risk for death in more than 10% to more than 1% of using population. The rest two outcomes require hospitalization for more than 2 days or incapacity for more than 7 days.

Table 2. *Seriousness (as per CIOMS and Working group IV) and outcomes (as per Benicou scale) of adverse events*

Reported adverse event	**Seriousness (CIOMS IV)[I]**	**Outcome (Benicou scale)[II]**
Ischemic strok	8.5 (maximum level seriousness)	6
Ventricular fibrillation	6.5	5
Severe rhabdomyolysis	6	4
Systolic blood pressure, diastolic blood pressure and heart rate were higher for up to 5 hours after a single dose of bitter orange versus placebo	5	3
Serious cardiovascular adverse events	5	2

[I]CIOMS IV: 7.5+ very serious; 5-7.5 Serious; 2.5-5 fairly serious; < 2.5 least serious

[II]Benicou – Category 6: Death in more than 10%; Category 5: Death in 1-10%; Category 4: Death in less than 1%; Category 3: Hospitalization for more than 2 days or incapacity for more than 7 days; Category 2: Hospitalization for more than 2 days or incapacity to 7 days; Category 1: Any other outcome

Discussion

Our study revealed that there is a little evidence that synephrine and *C. aurantium* extract containing food supplements are effective for weight loss. The performed trials are not sufficient to support such strong claims. The weight loss effect cannot be attributed to synephrine or *C. aurantium* alone as in some of the trials both groups received exercise programs and advices from dieticians. No standard dose exists and there are many differences among the regimens used in the trials.

On the other hand the seriousness of the reported adverse events and risk for death are very high for the consumers. This fact supported with the lack of any precaution measures for the users in the leaflets defines the synephrine or *C. aurantium* food supplements as dangerous products.

Our study supports the results reported in similar analysis that there is a necessity for tight control of the food supplement distribution and information provided to the public.

Conclusion

Although some evidences regarding the efficacy of synephrine and/or *C. aurantium* extract are promising, there is a need of more investigations in order to support the claims.

The information provided by the manufacturers of such supplements is often not clearly indicating the presence of doping substances, significant adverse reactions and interactions.

There is need for tight control by the relevant authorities for justification of product claims in the light of available scientific data on safety and efficacy for synephrine and *C. aurantium* extract.

It is very necessary that physicians and pharmacists obtain up-to-date information in order to justify the claims and safety of food supplements for weight loss, as well as to possess a reliable way for their safety evaluation.

Finally, the consumers should also inform their general practitioner or pharmacist in case they administer such supplements in order to avoid adverse event and possible drug-food supplement interactions.

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