University of Szeged

Faculty of Pharmacy

Institute of Pharmacognosy

Evaluation of medicinal plant-based products used for weight loss

PhD. Thesis

Dorottya Koncz

Supervisors:

Dezső Csupor DSc.

Barbara Tóth PhD.

Szeged, Hungary
2023

THE THESIS IS BASED ON THE FOLLOWING PUBLICATIONS:

I. **Koncz, D**., Tóth, B., Roza, O., & Csupor, D. (2021). A Systematic Review of the European Rapid Alert System for Food and Feed: Tendencies in Illegal Food Supplements for Weight Loss. *Frontiers in pharmacology*, *11*, 2465. IF: **5.988**

II. **Koncz, D**., Tóth, B., Bahar, M. A., Roza, O., & Csupor, D. (2022). The Safety and Efficacy of *Citrus aurantium* (Bitter Orange) Extracts and p-Synephrine: A Systematic Review and Meta-Analysis. *Nutrients*, *14*(19), 4019. IF: **6.706**

The cumulative impact factor of the publications related to thesis: 12.694

OTHER PUBLICATIONS RELATED TO THE THESIS:

I. **Koncz, D**., Tóth, B., Kiss, T., Roza, O., & Csupor, D. (2021). *Acacia rigidula* versus other *Acacia* taxa: An alarming issue in the European novel food regulation and food supplement industry. *Acta Pharmaceutica Hungarica*, *91*(2), 67-74.

II. **Koncz, D**., Tóth, B., & Csupor, D. (2021). Fogyasztószerként használt étrend-kiegészítők: Minőségi problémák az Európai Unióban. *Gyógyszerészet*, *65*(11), 671-675.

III. **Koncz, D.** (2021). Reports of illegal food supplements for weight loss in the European Rapid Alert System for Food and Feed (RASFF). *In: Symposium of Young Researchers on Pharmacognosy* (Book of Abstract), 17.

IV. **Koncz, D**. (2022). Dangerous and Potentially Dangerous Components of Weight Loss Products. *In: Symposium of Young Researchers on Pharmacognosy* (Book of Abstract), 15.

V. **Koncz, D**., Tóth, B., Roza, O., & Csupor, D. (2020). In: *9th Interdisciplinary Doctoral Conference 2020* (Book of Abstracts), 108.

TABLE OF CONTENTS

ABBREVIATIONS

4-HMP	Methyl-synephrine HCl, oxiflorine
5-HT2C	5-hydroxytryptamine
AMPK	Adenosine Monophosphate-activated Protein Kinase
ANSES	The French Agency for Food, Environmental and Occupational Health & Safety
API	Active Pharmaceutical Ingredient
ATP	Adenosine triphosphate
BMI	Body Mass Index
BP	Blood Pressure
CA	*Citrus aurantium*
CI	Confidence Interval
CGA	Chlorogenic Acid
CLA	Conjugated Linoleic Acid
DBP	Diastolic Blood Pressure
DDI	Drug-drug Interaction
DNP	2,4-dinitrophenol
EE	Energy Expenditure
EEA	European Economic Area
EFSA	European Food Safety Agency
EGCG	Epigallocatechin-3-gallate
EMA	European Medicine Agency
EU	European Union
FA	Fatty Acid
FDA	U.S. Food and Drug Administration
GCE	Green Coffee Extract
GLP-1	Glucagon-like Peptide 1
GM	Glucomannan
HCA	(-)-Hydroxycitric acid
HMPC	Committee on Herbal Medicinal Products
HR	Heart Rate
MD	Mean Difference
mmHg	Millimetres of Mercury
m-synephrine	*Meta*-synephrine (phenylephrine)
NA	Noradrenaline
NE	Norepinephrine
NK	Not Known
NR	No Reports
POMC	Pro-opiomelanocortin
PPA	Phenylpropanolamine
p-synephrine	*Para*-synephrine
QT	Measurement made on electrocardiogram
RASFF	Rapid Alert System for Food and Feed
RCT	Randomized Controlled Trial
RER	Respiratory Exchange Ratio
SBP	Systolic Blood Pressure
SCOUT	Sibutramine Cardiovascular Outcomes Trial
SD	Standard Deviation
SUKL	State Institute for Drug Control
T2DM	Type 2 Diabetes Mellitus
UL	Upper Limit
VO_2	Oxygen Consumption
WHO	Word Health Organization

1. INTRODUCTION

Finding safe and efficient methods to lose weight and prevent obesity, which has become a global epidemic that has increased morbidity and mortality, are of utmost importance.[1] To reverse unintended changes in body composition, lifestyle and dietary adjustments are generally advised; nevertheless, it is well known that in this case it is much easier said than done. Therefore, the majority of those who struggle with obesity yearn for quick and secure solutions; yet, there are few, if any, medicines that can address this problem in the long run without having negative side effects.[2] Several medicines have been withdrawn due to safety issues, and only a few active pharmaceutical ingredients (APIs) are marketed for weight loss and these can only be used in only in severe cases, like obesity and coexisting metabolic disorders.[2,3] Since medicines are not easily available in this indication, patients prone to try alternative solutions. Therefore, it is not surprising that obese patients turn to readily products regardless to their questionable quality, and the popularity of food supplements for weight loss management is increasing.[4,5]

This phenomenon gives a rise to several problems including patient safety. It has been proven that food supplements marketed for weight loss frequently contain illicit sympathomimetic drugs that are concealed to increase efficacy. Another common way to increase the efficacy is to use an ingredient above its allowed upper limit. Therefore, the actual composition of several weight loss products tends to differ from that on the label. Due to the flaws in the regulation of food supplements, these products may also be contaminated (e.g. with heavy metal, microorganisms, and pesticides).[6] Moreover, the lack of a clinically validated safety and efficacy profile raises doubts about the efficacy of a number of herbal ingredients.

The RASFF (Rapid Alert System for Food and Feed), a crucial tool for providing important information about unlawful goods, issues the notifications regarding counterfeit food supplements.[7] Reviewing the RASFF system allows to map current counterfeit tendencies and to collect the main adulterants occurring in weight loss supplements. Data extracted from the RASFF enables to categorize the most common quality issues.

2. AIMS OF THE STUDY

The aim of this work was to

- systematically review the European Rapid Alert System for Food and Feed (RASFF) reports to map the tendencies in food supplements / illegal products that are used to promote weight loss,
- based on the warnings collected via the RASFF, make a conclusion to find which unauthorized substances are dominating the market,
- to mark the mainstream signals as a public health issue, to initiate possible solutions to reduce counterfeit,
- to summarize the available and previously withdrawn active pharmaceutical ingredients in the European Union,
- to collect the most popular herbal food supplements and summarize their safety and efficacy,
- to compare the attributes of synephrine and ephedrine (a previously banned food supplement ingredient) in a systematic review, and
- to conduct a meta-analysis on synephrine to determine its proper utilization based on scientifically established results.

3. LITERATURE OVERVIEW

3.1. Obesity

Obesity is globally a growing public health issue; over the past 40 years the number of affected people has tripled.[8] Not only has the prevalence of obesity increased, but the average body mass index (BMI) of the global population has also risen by an average 0.4–0.5 kg/m^2 in every ten years.[5,9] Based on World Health Organization (WHO) estimates, nearly two billion persons had a BMI of above than 25.0, and more than 650 million of these adults were considered obese (BMI ≥ 30.0) in 2016.[10,11] Obesity has become an epidemic due to several reasons including sedentary lifestyle, increased access for high-energy foods and overconsumption of simple carbohydrates and sugar.[12,13] Family history and genetics is another susceptible risk factor for obesity. A cross-sectional study found a link between the BMI of schoolchildren and the AA [at-risk for obesity] genotype of the rs9939609 polymorphism. Those who had an obese mother ($p < 0.001$), an obese maternal or paternal grandmother ($p = 0.047$), or an obese paternal grandfather ($p < 0.001$) were more likely to be overweight or obese.[14] According to *Corica* et al.[15], cardiometabolic disorders and a family history of obesity are significant risk factors for premature obesity in children and are linked to the level of obesity. Based on specific family and twin studies, genetic variables account for between 40 and 70 percent of severity of obesity in humans.[16,17] The role of microenvironment and gut microbiome is also widely discussed and may represent a novel targets for the treatment of obesity.[18] The gut microbiota is hypothesized to regulate the process of energy balance. Specific environmental stressors that the gut microbiota is exposed to can throw off the energy balance of the body and eventually cause obesity.[18,19] It is very likely that obesity and depression are linked.[20,21] A meta-analysis showed a significant correlation between depression and obesity in the overall population.[21] Numerous comorbidities, such as cardiovascular (i.e. heart disease, hypertension) and cerebrovascular (i.e. stroke) disorders are assumed to be linked to obesity.[1] Type 2 diabetes mellitus (T2DM) and degenerative musculoskeletal disorders (such as arthritis) are more common in overweight and obese people than in those with a normal body mass index (BMI).[1,22] Additionally, obese people are more likely to develop malignant tumours and Alzheimer's

disease.[1] By the end of this decade, more than half of the world's adult population will be obese or at least overweight, if radical alterations will not be applied.[23]

3.2. Treatment of obesity

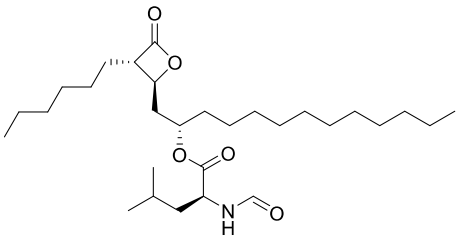
Dietary restrictions and increased physical activity are essential lifestyle modifications that help people lose weight, but because so many obese people discontinue their new lifestyles soon after starting them, the results are rarely long-lasting.[24] Numerous pharmaceuticals have been approved to promote weight loss throughout the last century,[25] however, for this indication, the European Union (EU) currently offers just some APIs and one combination product.[26] The most promising pharmacons are glucagon-like peptide-1 agonists (semaglutide, liraglutide). Naltrexone/bupropion are still under additional monitoring, and phentermine is available only in the Czech Republic, whereas orlistat has been approved by the European Medicines Agency.[26,27] Due to safety concerns several other medicines are no longer available on the market. Alternative approaches of treating obesity are widely searched. Food supplements, which are readily available on the market, are utilized frequently for this purpose.[5]

Orlistat (**1**) has been approved for obesity management in 1998 (**Annex 1**), as the first selective, irreversible gastric and pancreatic lipase enzyme inhibitor.[28,29] Its mechanism of action involves the inhibition of dietary fat lipolysis and absorption of dietary fat.[30] Orlistat is a prescription-only medicine in the European Union. Apart from modest side effects (e.g. abdominal pain, diarrhoea, faecal spotting, and steatorrhea), the use of orlistat was also linked to severe adverse responses (e.g. subacute liver failure, cholelithiasis and cholestatic hepatitis). Because orlistat interferes with the absorption of other medications and fat-soluble vitamins, the long-term safety of orlistat is questionable.[31]

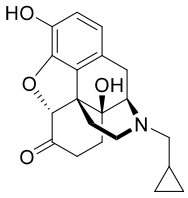
A combination therapy for weight control that contains naltrexone (**2**) and bupropion (**3**) was approved after additional clinical trials confirmed its safety.[32] The combination therapy involves naltrexone which is an opioid antagonist on the μ-opioid receptor and reduces appetite by inhibiting β-endorphin-mediated autoinhibition of POMC (pro-opiomelanocortin) neurons.[33-35] The activity of POMC cells in the arcuate nucleus are stimulated by the antidepressant bupropion, resulting in anorectic effects.[36] Based on a human study[34], this

combination may be used as a suitable treatment adjunct to lifestyle changes because it increases fullness, decreases appetite, and energy expenditure, which aids patients in achieving their weight reduction objectives.[26,37] The initial clinical trials mostly examined the adverse cardiovascular effects of the combination.[37,38] In patients with uncontrolled hypertension, the combination of naltrexone and bupropion should not be used; nevertheless, the potential consequences of this combination on the patients' cardiometabolic parameters are not fully established.[39,40] Based on the clinical trials on this topic, participants in the verum group frequently experienced nausea, headache, constipation, dizziness, vomiting, and xerostomia as side effects.[41] Bupropion raises blood pressure both on its own and in combination with naltrexone, so treatments including its administration should only be started in individuals whose blood pressure is well-controlled.

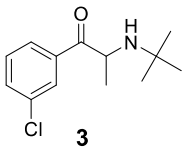
Phentermine (**4**) was another promising drug to promote weight loss. It acts on hypothalamic POMC neurons by inhibiting the norepinephrine transporter.[42] In 1956, phentermine was approved for treating obesity in Europe (**Annex 1**), and for decades, it was a commonly prescribed medication.[43] However, due to its negative effects, the EMA decided to withdraw the marketing approval of phentermine in 2012. Considering the published literature, prolonged use of the chemical may have negative effects on the cardiovascular and nervous systems.[44] Nevertheless, according to the approval of the national competent authority, phentermine resinate is marketed in the Czech Republic in the form of modified-release capsules.[27]



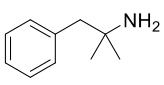
1



2



3



4

Liraglutide was initially utilized to treat T2DM because of its glucagon-like peptide-1 (GLP-1) receptor agonist activity.[45] Liraglutide has been a promising drug in the treatment of T2DM since it enhances the cardiovascular health and outcome of patients.[46] GLP-1 analogues have gained approval as medications for weight control since it has been demonstrated in human trials that they facilitate weight loss.[47] Mechanism of action of liraglutide include increase of insulin and decrease of glucagon secretion, delayed stomach emptying and appetite control.[48] The European Medicine Agency (EMA) approved liraglutide as a supplement to complete a lifestyle program to promote weight loss.[26,49] In human clinical trials, gastrointestinal symptoms (such as nausea and vomiting, increased risk of pancreatitis), and an elevated heart rate were the most often reported side effects.[46]

Liraglutide is available as an injection; however, semaglutide, another GLP-1 receptor agonist, can be used *per os.*[50] Recently, subcutaneous semaglutide applied once weekly for the treatment of T2DM received approval from both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA).[51] With the administration of 2.4 mg semaglutide once a week for 68 weeks the estimated change in mean bodyweight from baseline was -9.6% in the treatment group (n=404) *vs* -3.4% in the placebo group (n=403) and -9.7 kg (n=388) *vs* -3.5 kg (n=376) respectively.[52] It is assumed that semaglutide has one of the most pronounced effects on weight loss to date, and given to that it improves cardiovascular risk factors and physical performance, it is a very promising drug for the treatment of obestiy.[53] Orally used semaglutide is also safe and effective in lowering systolic blood pressure, body weight, and blood sugar levels.[54] However, gastrointestinal side effects may occur quite often. Clarifying its long-term safety and comparative performance with other antidiabetic medications need more research.[54]

3.3. Withdrawn medicines in the European Union

Amphetamine and its derivatives, such as phenylpropanolamine, fenfluramine, and dexfenfluramine were used to treat obesity in the 1930s.[55] Amphetamine derivatives stimulate the release of norepinephrine and dopamine in the satiety centres of the hypothalamus and limbic regions as part of their weight loss mechanism of action.[56] The anorexigenic effects of amphetamine derivatives last for a few hours, although tolerance sets in within a short period of time (a few weeks). The use and abuse of amphetamines frequently causes cardiovascular

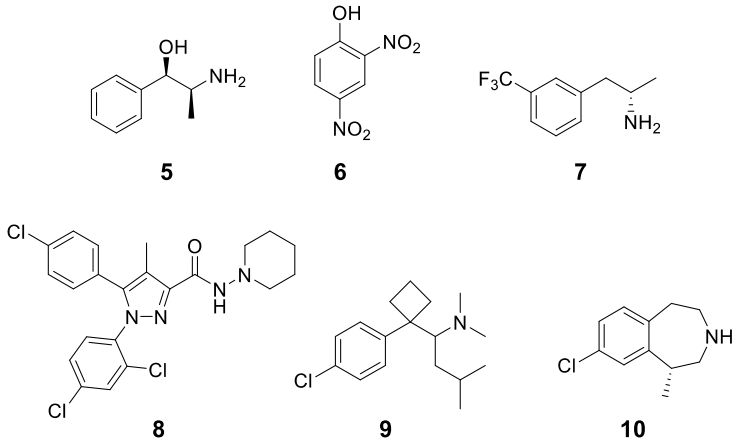
side effects.[57] Due to safety concerns and the rapid development of tolerance, amphetamine was removed from the European market in 1968 (**Annex 2**).

Without a prescription, phenylpropanolamine (PPA, **5**) was widely used to treat coughs and colds and commonly administered as an appetite suppressant for weight loss.[58] Chemically, PPA is related to the amphetamine-like anorectic agents.[59] PPA has been shown to help people lose weight, although its exact mechanism of action is not entirely understood.[60] The medicine is still available in certain European countries to treat rhinitis even though its safety and efficacy profile is debatable. The major safety concern is the connection between PPA intake and stroke.[58]

Initially used in explosive mixes, the substance 2,4-dinitrophenol (DNP, **6**) had rapidly became highly promoted in slimming products after its effects on the body weight was discovered in 1933.[61] DNP increases basal metabolic rate, which promotes weight loss.[62] DNP was effective, but serious adverse effects occurred so frequently that it was withdrawn from the market, and it was labelled being 'extremely dangerous'.[63-65] The mode of action of DNP is linked to its harmful effects. By decoupling oxidative phosphorylation, DNP causes the body to enter a hypermetabolic state, where the extra energy is converted to heat energy in the mitochondria. As a result, the hypermetabolic condition is followed by uncontrollable thermogenesis that results in hyperthermia and an unfavourable increase in body temperature that is linked to systemic responses.[66] Despite the fact that DNP was no longer prescribed after 1938, the drug was still being used because case reports of DNP-related deaths continued to appear even after the drug was withdrawn from the market.[65] DNP is currently marketed illegally under a variety of different names.[64]

The active metabolite of the prodrugs fenfluramine and dexfenfluramine, (+)-norfenfluramine (**7**) causes weight loss and is a strong agonist on 5-hydroxytryptamine (5-HT_{2C}) receptors.[67,68] Despite the fact that their long-term safety had not been established, fenfluramine and its (S)-isomer, dexfenfluramine, were both used in monotherapy, the former for short-term weight management and the latter for long-term weight management.[69] Dexfenfluramine however had rather alarming side effects; a case-control research found that it increased the prevalence of cardiovascular disorders and was linked to pulmonary hypertension.[70] As a result, both

medications as well as the so-called fen-phen formulation (a mix of fenfluramine and phentermine) were taken off the market in 1997 due to safety concerns.[69,71,72]



In 2006, rimonabant (**8**), the first cannabinoid receptor type 1 (CB1-receptor) antagonist, was approved in the EU.[73] It was originally thought to be a promising drug because numerous studies had demonstrated its beneficial effects on weight loss and on improved metabolic syndrome measures.[74] Finally, because the use of rimonabant was associated with a number of psychiatric side effects (i.e. anxiety, depression, and suicide ideation), in the EU, the EMA withdrew its authorisation in January 2009.[75]

Sibutramine (**9**) is originally used as an antidepressant that inhibits the reuptake of neurotransmitters serotonin (5HT)- and noradrenaline (NA). Later it was found to be able to reduce appetite.[76] Concerns about the safety of sibutramine were raised following reports of elevated diastolic and systolic blood pressure and pulse rate.[77] Consequently, the so-called Sibutramine Cardiovascular Outcomes Trial was carried out to evaluate its safety (SCOUT).[78] In this trial, patients with a history of cardiovascular illness were randomized to assess the safety of sibutramine. The EMA consequently determined that the risk-benefit ratio for sibutramine was not acceptable and recommended withdrawing all marketing authorizations for medications containing sibutramine in Europe.[79] The market authorisation of sibutramine was suspended in 2010 after being approved in 2001.[80]

The 5-HT_{2C} receptor agonist lorcaserin (**10**), which was authorized for the long-term treatment of obesity, was meant to be used in a combination with a low-calorie diet and increased

physical exercise.[81] Only one year after receiving marketing approval, in 2013 **(Annex 3),** the marketing authorization holder formally informed the EMA's Committee for Medicinal Products for Human Use (CHMP) of suspending the marketing authorization for lorcaserin because, based on the opinion of the CHMP, the medication's advantages did not outweigh its risks (e.g. depression, valvulopathy).[82] Patients receiving lorcaserin had a significantly higher risk of developing depression.[83] Long-term use may be linked to an increased risk of cancer.[84]

To sum it up, several medications which were previously used to manage body weight are no longer available on the market due to their dangerous side effects. Since there are currently only a few therapeutic options available to help weight loss, and all of these are prescription-only products, there is a clear need for effective products to deal with this problem. Customers are seeking for easily accessible food supplements for quick fixes, and this business is responding by growing internationally.

3.4. Natural components in food supplements for weight loss

A recent study showed that the most widely advertised natural compounds for weight-loss are chitosan, glucomannan, capsaicin, carnitine, and conjugated linoleic acid (CLA).[85] Other popular herbal compounds in Europe, include *Camellia sinensis* (L.) Kuntze, *Garcinia gummi-gutta* (L.) N.Robson (syn. of *Garcinia cambogia* Roxb.), the unroasted green seed of *Coffea arabica* L.,[86,87] *Hoodia gordonii* (Masson) Sweet ex Decne., *Stevia rebaudiana* (Bertoni) Bertoni, and *Vachellia rigidula* (Benth.) Seigler & Ebinger (syn. of *Acacia rigidula* Benth.) which also was a regular component of weight loss products in the RASFF warnings. The extract of bitter orange (*Citrus* × *aurantium* L.) and its active constituent *p*-synephrine is also a common ingredient in weight loss and pre-workout supplements, and it is frequently used to replace ephedrine.[88]

Chitosan may help with weight management by reducing dietary fat and cholesterol absorption.[89,90] Additionally, it may increase fat excretion, which would result in weight loss without changes in diet.[89] The effects of chitosan on body weight, serum lipids, and blood pressure were investigated in a meta-analysis of 14 randomized controlled trials (RCTs).[90] Based on to the literature findings, chitosan use as a food supplement for up to 52 weeks may promote weight loss (average -1.01 kg). Besides having a modest impact on body weight,

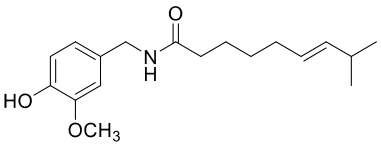
chitosan consumption improved serum lipid profiles and significantly lowered systolic and diastolic blood pressure (-2.68 mmHg, and -2.14 mmHg, respectively). Based on human studies, using chitosan for a short period of time is safe.[91] Moderate side effects, such as flatulence, constipation, indigestion, nausea, and heartburn may occur.[92] Chitosan may interact with warfarin and affect the absorption of fat-soluble vitamins (such as vitamins A, D, E, and K**)** to some extent; however, its effects on faecal fat excretion have not yet been thoroughly established.[93,94]

Amorphophallus konjac K.Koch tubers are the used to extract glucomannan (GM) utilized in weight-loss products.[95] GM is a hemicellulose type polysaccharide that enhances energy loss through faecal excretion, and it boosts mastication efforts and delays gastric emptying afterward. Additionally, increased plasma cholecystokinin levels cause cephalic- and gastrointestinal-phase satiety signals.[87,92] According to a meta-analysis, taking GM (1.2–15.1 g/day) on a daily basis for five weeks enhances the metabolic profile of patients but has minimal effects on the body weight (WMD: −0.79 kg).[96] However, *Zalewski* and *Szajewska*, 2015 presented conflicting findings, indicating that short-term usage of GM may cause a slight weight loss in otherwise healthy overweight or obese people but has no significant impact on BMI.[97] The use of GM was linked to mild gastrointestinal side effects (bloating, diarrhoea).[98]

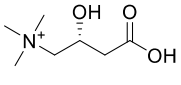
Consuming meals rich in capsaicin (**11**) may help regulate weight by preventing obesity[99] as capsaicin influences lipid oxidation and energy expenditure.[99-101] Additionally, healthy women who routinely consume chili peppers have a slightly lower body weight than those who are not regular users.[102,103] Based on a meta-analysis involving eight trials and 191 participants, those who took 2 mg of capsaicin before each meal consumed 74 less calories than the control group. This suggests that capsaicin may help people maintain their weight by lowering their overall energy intake.[100] However, it only moderately affects thermogenesis and fat oxidation, and its long-term effectiveness is debated.[104] Although it may induce mild-to-moderate gastrointestinal side-effects, sweating, flushing, and rhinorrhoea, capsaicin is safe at moderate dosages.[105] Additionally, capsaicin may interfere with antihypertensive agents.[106]

Long-chain fatty acids (FAs) are transported by carnitine (**12**) into the mitochondria where they are converted into energy by the process known as β-oxidation. Carnitine contributes in the elimination of toxic substances from the cells.[107] The L isomer of carnitine is used to improve weight reduction.[108] In a systematic review and meta-analysis, the results of nine RCTs including 911 patients were evaluated.[109] Participants who received carnitine (in doses ranging from 1.8 g/day to 4 g/day) lost significantly more weight (about -1.33 kg) and had significantly lower BMIs (about -0.47 kg/m^2) than those who received the control treatment. The outcomes showed that the effects of carnitine on weight loss decrease over time. L-Carnitine is well tolerated up to 15 g/day, only mild side effects such occasional diarrhoea, gastralgia, and nausea were reported.[110]

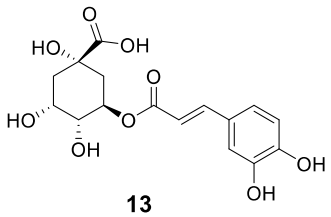
Conjugated linoleic acid (CLA) and its isomers variably affect the expression of the genes involved in lipid metabolism by activating various nuclear receptors.[111] Beef meat and dairy products are the natural sources of CLA; however, dietary supplements can also contain CLA.[112] A meta-analysis of human studies revealed that the effect of 3.2 g/day of CLA on weight loss and body fat-reduction was modestly effective compared to the placebo.[113] On the contrary, in some trials, the intake of CLA did not result in significant weight loss.[85] Therefore, the effectivity and safety of CLA dietary supplements should be further evaluated.[114] Because CLA interfered with glucose metabolism in animal studies (e.g. increased insulin resistance in mice) and changed liver function, causing lipodystrophy, these effects should also be examined in human trials to clear out any safety concerns.[115]



11



12



13

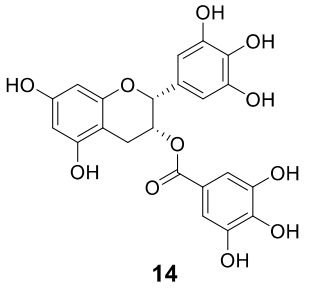
Because of the thermolability of chlorogenic acids (CGAs, **13**), unroasted *Coffea arabica* seeds are better sources of these compounds, which are practically absent in roasted coffee.[116] Due to the presence of CGA in green coffee, it may be used to help people lose weight.[117] Based on the available literature data, green coffee extracts high in CGA lower blood cholesterol and glucose levels, blood pressure, as well as the risk of developing certain

cardiovascular diseases.[118] The effects of chlorogenic acid in the treatment of metabolic syndrome are mostly connected to its anti-oxidant, anti-inflammatory, antilipidemic, antidiabetic, and antihypertensive abilities.[119] CGA stimulates the glucose uptake in both insulin-sensitive and insulin-resistant adipocytes.[120] Moreover, it also increases insulin secretion and inhibits the activities of α-amylase and α-glucosidase.[121,122] Preclinical studies suggest, that the effect of CGA on body weight partly relies on the activation of adenosine monophosphate-activated protein kinase (AMPK).[123] A significant reduce in body weight was achieved by consuming green coffee extract (GCE), according to a meta-analysis of three RCTs with a combined total of 142 individuals.[124]

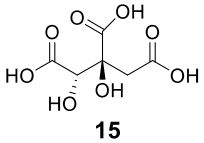
Green tea is made from the unfermented leaves of *Camellia sinensis*. Its active ingredients include catechin polyphenols, such as epicatechin, epigallocatechin, epicatechin-3-gallate, and epigallocatechin-3-gallate (EGCG, **14**). From these substances, EGCG is found in the highest concentration in green tea, and this substance has the most significant pharmacological effects.[125] Another pharmacologically important active component in green tea is caffeine.[126] It was discovered that those who typically consume low doses of caffeine benefited the most from a combination of green tea and caffeine in managing body weight. Caffeine increase thermogenesis and fat burning while decreasing leptin levels.[127,128] As a result, consumption of green tea may result in body weight reduction.[128] Additionally, catechins, particularly EGCG, inhibit catechol-*O*-methyltransferase (COMT), which promotes the fat oxidation.[128] Based on a meta-analysis of human trials using green tea, EGCG-containing extracts have a considerable impact on weight reduction and its maintenance (WMD: −1.31 kg; duration at least 12 weeks). The effect of caffeine intake on body weight was not significant when data from studies only with high regular caffeine intake were analysed. Although the study populations for these two groups were different: Asian individuals received low caffeine doses while Caucasian participants received moderate-to-high caffeine doses. Conflicting findings may also be due to the heterogeneity of the included studies.[129] Green tea extracts are frequently found in weight-loss products, although there are concerns about their high (>100 mg/day) EGCG content being hepatotoxic.[130]

Garcinia cambogia contains (-)-hydroxycitric acid (HCA, **15**). This substance has been shown to inhibit adenosine triphosphate (ATP) citrate lyase.[131] When patients follow a so-

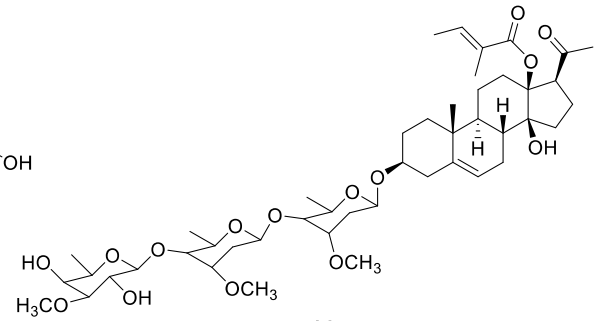
called lipogenic diet with high amounts of carbohydrates, the above-mentioned enzyme is inhibited, which limits the availability of acetyl coenzyme A (acetyl-CoA) units required for fatty acid synthesis and lipogenesis.[132-134] The substance restricts the production of FAs, lipogenesis, and reduce appetite, which promotes weight loss.[135] Despite its intriguing mechanisms, clinical research has had conflicting results.[136] A meta-analysis of nine RCTs showed that HCA had a significant effects on weight loss when compared to placebo.[137] Participants in the included studies consumed 1–2.8 g of HCA daily for periods ranging from 2 to 12 weeks. Recent incidences of acute liver damage have been linked to a *Garcinia cambogia*-allegedly-containing product.[138,139] Acute liver failure and symptomatic acute hepatitis were also described in addition to mild side effects (transient and moderate enzyme elevations.[139] Although the prevalence of hepatic side effects is unknown, it appears to be low (1:10,000). By altering insulin sensitivity, enhancing gluconeogenesis, and raising the production of ketone bodies, HCA may have an impact on glucose homeostasis.[136,140]



14



15



16

Hoodia gordonii is a succulent cactus which was traditionally consumed by indigenous South Africans for its ability to suppress appetite.[141] Since *H. gordonii* has never been used as a food or food ingredient prior to May 15, 1997, it could only be marketed in Europe following an appropriate safety assessment.[142] P57 (**16**), an oxypregnane glycoside, is thought to be the active ingredient in *H. gordonii* that suppresses appetite. It was reported that P57 enhanced ATP synthesis in the hypothalamus following intracerebroventricular dosing.[143] The Cochrane Library, ClinicalKey, PubMed/Medline, and Google Scholar databases did not yield any published, peer-reviewed meta-analyses of RCTs evaluating the effectiveness of *Hoodia*. The effects of *H. gordonii* weight loss was compared to placebo in one trial. In this study 25 participants received 1,110 mg *H. gordonii* daily while 24 received placebo throughout the

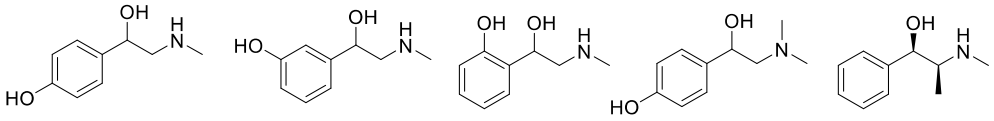
15-day study period.[144] There were no significant changes in the body weight and there were no major side effects; however, participants in the verum group reported nausea, vomiting, and changes in skin sensation. In the verum group, there was a significant rise in blood pressure, heart rate, and in bilirubin and alkaline phosphatase levels. There are other recent reports of the above-mentioned side effects (i.e. elevated blood pressure and heart rate).[145]

Native Americans in South America have traditionally utilized the plant *Stevia rebaudiana* to sweeten their food and as a traditional medicine (e.g. herbal tea to treat heartburn).[146] *S. rebaudiana*-derived glucosides are about 300 times sweeter than sucrose. Low- and no-calorie sweeteners like *S. rebaudiana* may serve as alternatives to reduce sugar intake,[147] and this is the reason for its use in product offered for those who would like to lose weight. Overall, consuming *S. rebaudiana* appears to be safe.[148] Since only steviol glycosides from stevia, commonly known as stevia extract, were authorized in the European Union prior to 2017, stevia emerged as an unapproved novel food component in RASFF before 2018.[149,150] Stevia leaves and preparations made from stevia leaves were authorized only in 2017, under the novel food legalization procedure.[150,151] Recently it is covered by the General Food Law, which also regulates all other food products and ingredients.[150,152] According to the novel food catalogue tea, herbal and fruit infusions containing *S. rebaudiana* leaves are considered as general food (not as novel food) and therefore can be marketed in the EU.[142] Regulation (EU) 1131/2011 authorized steviol glycosides as a sweetener in 2011 with the number 'E 960' in the Union list of food additives.[149,153] Currently, the use of stevia extract as a sweetener or as flavoring compound fall in the context of Regulation (EU) 1131/2011, Regulation (EU) 1156/2021 and Regulation (EU) 2016/1814 in harmony with Regulation (EC) No 1333/2008[154] on food additives or Regulation (EC) No 1334/2008 on flavorings respectively.[142,149,155-157]

Consumption of *A. rigidula* can be potentially dangerous, because it contains significant levels of toxic azotoids.[158] Regarding its safety and efficacy, a thorough literature search in numerous databases (PubMed/Medline, the Cochrane Library, ClinicalKey, and Google Scholar) yielded no human studies.[159] Since *A. rigidula* is currently not considered a novel food in the European Union, it cannot be sold in food supplements. *Acacia senegal* (L.) Willd.

(syn.: *Acacia verek* Guill. & Perr.) and *Acacia arabica* (Lam.) Willd. (syn.: *Acacia nilotica* (L.) Willd. ex Delile) are approved as novel food ingredients.[142]

The protoalkaloid *p*-synephrine (**17**), which is most often obtained from the immature fruit or peel of the bitter orange (*Citrus aurantium*), is frequently utilized in products for weight reduction and athletic performance.[160] However, its efficacy and safety have not been established.[161] There are three different positional isomeric variants of synephrine [para, meta (**18**) and ortho (**19**)].[162] Most studies agree that only para-synephrine (*p*-synephrine) can be detected in bitter orange fruits.[163-165] Food supplements have been found to contain illegally a synthetic *p*-synephrine derivative, methyl-synephrine (**20**).[166-169]



17 **18** **19** **20** **21**

p-Synephrine has attracted a lot of interest as the initial ephedrine substitute in weight loss products since the use of ephedrine (**21**) in dietary supplements was forbidden in numerous European and American countries.[165,170-172] In terms of its structure and mechanism of action, synephrine is comparable to ephedrine; however, because it is less lipophilic, it can cross the blood-brain barrier at a lesser extent.[160,173-175] The use of ephedrine is linked to an increased risk of stroke, hypertension, and myocardial infarction[165,176], although when taking *p*-synephrine, such pronounced effects on the cardiovascular system are usually not expected. However, serious side effects related to synephrine ingestion also include cardiac adverse events, such as hypertension, tachyarrhythmia, variant angina, cardiac arrest, QT prolongation, ventricular fibrillation, myocardial infarction, and even sudden death[177]; but the incidence rate is unknown. Due to its thermogenic and sympathomimetic qualities, *p*-synephrine (hereinafter referred to as synephrine) is utilized in pre-workout supplements to enhance performance and to induce weight reduction.[177,178] The use of synephrine in food supplements is debated due to its well-known adrenergic effects influencing the cardiovascular system.[179] Despite the fact that there is no regulation limiting the amount of synephrine and other alkaloids in food supplements, each nation should be encouraged to determine the maximum level of synephrine in accordance with Directive 2002/46/EC.[180,181]

Because synephrine has a daily dose restriction in some countries, there have been reports in the RASFF about products containing more synephrine than allowed.[7] The French food safety authority (ANSES) came to the conclusion that intake levels of synephrine from food supplements must be kept below 20 mg/day and that taking synephrine with caffeine is not advisable.[182]

3.5. Safety and quality issues related to food supplements

The fact that prior to commercialization there are no formal regulatory pre-approval criteria for food supplements gives unethical distributors and manufacturers the possibility to adulterate supplements by adding APIs or other counterparts to boost efficacy.[183,184] Since, compared to medicines, the regulation and control of food supplements is less comprehensive, the ratio of counterfeit (e.g., mislabelled and/or potentially dangerous products) might be higher.[5] Drug-drug interactions (DDIs) potentially occur when active pharmaceuticals and/or unauthorized herbal substances are hidden in food supplements. The effects of one drug altered by the co-administration of another potentially can cause serious health problems. Numerous variables, such as the patient's age, co-morbidities, and pharmacogenetics, affect the clinical response for concomitant medication. Due to the fact that illegal synthetic substances are often not labelled and hidden, DDIs can arise unexpectedly.[185] The replacement of prescribed medications and an erroneous sense of security during the advancement of major diseases are additional sources of harm to consumers' health.[186] Toxic contaminants may also occur in food supplements (e.g. heavy metals, microorganisms). These contaminants can also have serious side effects and may interact with other medications.[5] Allergenic substances might also not be labelled and remain hidden.[187]

The health of consumers may also be at risk from variations in the amount of some substances, whether they are below minimum or over maximum, as in the case of synephrine, which is particularly dangerous when combined with a high caffeine dosage.[88] Another relevant factor is that a person's nutritional requirements vary depending on their energy requirements (based on weight, height, etc.), and other physiological conditions (development stage, pregnancy and lactating). Furthermore, lifestyle factors like stress, alcohol consumption, smoking, and physical activity level could all affect dietary requirements.[188]

Unauthorized herbal products similarly pose a variety of hidden risks, since, natural origin does not ensure safety.[189] It is crucial to note that herbal compounds might interact with medications and that natural products can also result in adverse events. It is a myth that using herbal substances is always safe and without any risk.[190-193] Food supplements may also contain other unauthorized ingredients, such as unauthorized novel food ingredients, whose safety has not been scientifically established.[5] Summarily, the lack of scientific evidence for safety does not mean that the compound is safe. RASFF can be an effective tool to help risk minimization and proactively suggest solutions for this complex global issue in food supplement industry.

3.6. The RASFF system and legal framework

The RASFF was established to help the national competent authorities synchronize their actions and sharing information with one another in regard to the control of foods and feed that pose serious threats.[7] In the European Union, RASFF is used to help ensure that feed and food meet the very minimum standards for safety and quality. This platform was aimed to create a system for reporting concerns about food safety in the European Union. A member state should immediately alert the European Commission (EC) via RASFF when it is supposed that a food or feed poses a serious risk to the public's health. The members are required to notify the EC to protect the public's health when products are withdrawn from the market, recalled, or when quick action is required.[7] Additionally, they must report if they concurred with the responsible operator that a food or feed should not be distributed, and any action has been made due to serious risk. The same applies in the case if the product is despite of being controversial is still marketed under certain circumstances. Information sent through RASFF enables EU nations to respond to a hazard to public health posed by food or feed more quickly and effectively. Regulation (EC) No 178/2002, which establishes the European Food Safety Authority, specifies general principles and requirements of food law, and regulates procedures in food safety matters, which serves as the legal basis for the RASFF.[7,152] The procedure describes when a RASFF notification is necessary and specifies the system members. After the five primary processes have been completed, each RASFF member has a designated contact point that is in responsible of forwarding RASFF alerts to the Commission. (i) The suspected item had to undergo market or border inspection by food

or feed inspectors. They might have collected samples and verified the findings of the laboratory. (ii) The product is determined to be non-compliant and must be reported to the national system. (iii) The authority determines whether the problematic product belongs to the scope of the RASFF system and informs the national RASFF contact point. (iv) The national contact point submits the RASFF notification to the European Commission after verifying and completing it as required. It includes necessary documentation, such as analytical reports, and describes the findings and actions taken using a RASFF notification form. (v) Templates are primarily used to collect all relevant data on the RASFF report, as RASFF report must contain some crucial information. (i) The "origin" field provides the information that is currently available regarding the source of the concerned product(s); however, this does not imply that any discovered dangers are related to that origin. (ii) The action taken field shows the action that the notifying country has taken or ready to take at the time of notification. “No action taken” by the notifying country means that the product is not on the market in that country, although it may be available in other member countries and should be scrutinized. (iii) The "Distribution status" section shows potential market distribution ["in the European Economic Area (EEA)] for the product, which does not necessarily mean that the product is already available to consumers on the shelves, as this is frequently not the case.[7] In addition, the RASFF generally make information available to the public, but members of the network are not permitted to release any information that is officially considered private. In order to ensure that feed and food meet the minimum requirements for safety and quality, the European Union uses RASFF. Each RASFF member [the 27 national food safety agencies of the European Union and Norway, Liechtenstein, Iceland, and Switzerland, as well as the Commission Services of the European Commission, EFSA, and ESA (European Space Agency)] may identify an issue and take the necessary actions (such as withdrawing the product) to trigger the alert.[187]

The types of RASFF notifications can be alert; information; border rejections or news. The notification's objective is to provide all RASFF members the necessary information to confirm whether the enquired product is available on their market. Consequently, the nation will be supported to protect public health where it is required. It denotes situations in which immediate action is necessary due to a serious health risk (risk decision process). The RASFF is intended to be a crucial tool for the national competent authorities to coordinate their efforts

and notify one another regarding the control of food and feed that pose dangers for costumers.[7]

The new Novel Foods Regulation (EU) 2015/2283 aims to maintain a high level of food safety for European consumers while making it easier for food firms to introduce new and innovative foods to the EU market.[194] The list of approved novel foods in the European Union is contained in Commission implementing Regulation (EU) 2017/2470 of 20 December 2017 creating the Union list of novel foods in accordance with Regulation (EU) 2015/2283 of the European Parliament and of the Council on novel foods.[195] Use of a product that has been rejected under the Novel Food Regulation in any food or feed products is prohibited. Therefore, a safety assessment under the Novel Food Regulation is necessary before it may be placed on the market in the EU as a food or food ingredient. Action must be taken right away in case of the availability of an unapproved food supplement, and via RASFF, the national responsible authorities must warn every interested party involved in the control of food and feed that pose significant threats.[7]

4. MATERIAL AND METHODS

4.1. Analysis of RASFF data

Data from the RASFF portal were collected retrospectively. The filter in the portal was set for "dietetic foods, food supplements, fortified foods". Data from individual reports were entered [date, product, product category, notification type, origin (notified by), countries concerned, subject, action taken, distribution status and risk decision)]. Four main categories were created and sorted the notification records. The first was "A" for unauthorized ingredients; the second represented "B" for unsafe ingredients; and two others: "C" if there was a problem with the level of the ingredient (too high or too low) or "D" which meant other problems (e.g. mislabelling, taste disturbance). "A" category was handled differently than "C", and the results were analysed also separately. As part of the RASFF Portal, RASFF signals are categorized as alert, information notification, or border rejection. On the basis of the reported product's intended application, subcategories were constructed. The risks and adverse effects were also evaluated. Before January 1, 2020, all data from the reported supplements database, ranging from 1988 to 2019, were extracted. Each entry was individually reviewed. Descriptive analyses were performed using Microsoft Excel 2010 (Microsoft Excel, RRID:SCR_016137) for Windows (Microsoft Inc.), after categorizing RASFF signals.

4.2. Meta-analysis

4.2.1. Literature search and selection criteria

The Cochrane Library, PubMed, EMBASE, and Web of Science (WoS) databases were searched electronically. All databases were checked until August 17, 2022. The key term 'synephrine' was used in the search process. Following the CONSORT recommendations, this meta-analysis of eligible peer-reviewed articles was presented in compliance with the PRISMA statement. Trials were chosen if they met the following criteria: (1) they involved humans, (2) they compared known doses of orally administered synephrine with a placebo, an active control, or both, and (3) they were completed. The PICO (patients, intervention, comparison, outcome) format was used to accomplish this work as follows: P: adults; I: known *p*-synephrine dosage administered orally; C: placebo or control; and O: changes in

body weight, composition, cardiovascular, and metabolic markers (i.e., heart rate, blood pressure, body weight, body fat, fat mass, fat-free mass, fasting blood sugar level, and RER values). Our hypothesis was that synephrine promotes weight loss and that using it is linked to undesirable cardiovascular effects. This work is PROSPERO registered (359626). There were no restrictions on the number of patients who could participate or the amount of *p*-synephrine that could be administered. The included articles had to be accessed in English.

4.2.2. Data extraction and endpoints

Only clinical trials involving adults were included in this meta-analysis, as stated in the PICO. Findings related to the efficacy and safety of synephrine were collected from these clinical trials. The values that were available at least in three articles were chosen for the final analysis of the study endpoints. The final trials/outcomes of analysis could change as a result of statistical analysis. The primary author's name, publication year, study design, population, participant count, other medications used in the intervention group, synephrine regimen, and results were all taken out of individual studies.

4.2.3. Quality evaluations

The literature search was performed independently by two authors (D.K. and D.C.), and both authors read the full-text articles and extracted the relevant information out of the sources. The Cochrane Risk of Bias Tool, which includes the following domains: random sequence generation, allocation concealment, the blinding of participants and personnel, the blinding of outcome assessment, incomplete outcome data, selective reporting, and other scores of bias, was used performed by two of the authors (D.C. and B.T.) to analyse the risk of bias. Studies were classified as having a high (red), unclear (yellow), or low (green) risk of bias for each domain (**Annex 4 and 5**). Any disagreements finally were resolved by consensus. The Review Manager (RevMan) software from the Cochrane Training site in London, UK was used for generating risk of bias figures.

4.2.4. Statistical analysis

If an outcome was mentioned in at least three papers, it was chosen for the final analysis; nevertheless, subsequent attrition and particular time periods could change the examined

study and outcome number. A post-post analysis was conducted to evaluate the weighted mean difference (MD) and effect sizes (ESs) between test and control group values (synephrine vs control). The heterogeneity was assessed using Chi^2 or Tau^2 test. When there was any additional intervention(s) beyond synephrine, the varying study intervention arms were eliminated from the final analysis (mainly caffeine). In the case of subjects who consumed different amounts of caffeine, habitual low caffeine users were chosen compared to regular high caffeine users. The Review Manager 5.4.1 program was used to carry out the statistical analysis. When the p value was less than 0.05, the findings were accepted statistically significant.

5. RESULTS

5.1. RASFF notifications

2,559 records of food supplements with quality issues were included in the RASFF database's raw data set, and several of these products were marketed to assist weight loss (372, 14.54 %). 319 (12.5%) of the overall counterfeited weight loss aids were containing illegal unauthorized substances ("A" category). Of these slimming products, 202/319 (63.3%) contained synthetic weight loss pharmacons that were not approved. Erectile dysfunction medications and performance enhancers, which are not included in this article, were other often utilized adulterants. According to the aggregate reports taken from RASFF, the first alerts were made in 2003, and the number of recorded signals continued to rise until 2019 (especially in case of DNP). DNP was the most frequent adulterant in the anti-obesity products (113 out of 319, 35.4%). In the weight loss dietary supplement category, sibutramine was the second most common adulterant (69 products, 21.6%), and it was reported every year, as contrary to DNP, which was only reported in four distinct years, in 2003, 2017, 2018, and 2019. Phenolphthalein, a laxative with genotoxic and carcinogenic potential was the less common synthetic adulterant, with 20 reports. Less frequently reported unauthorized plant substances included *Vachellia rigidula* (in RASFF portal listed as syn.: *Acacia rigidula*) *Stevia rebaudiana* and *Hoodia gordonii* (**Figure 1).**

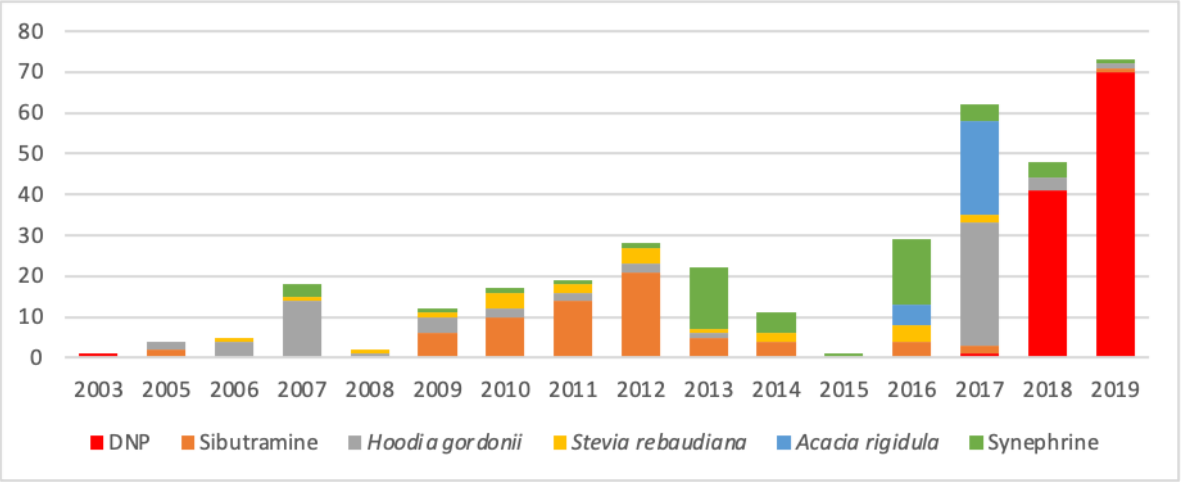


Figure 1. Notifications on weight loss food supplements in the RASFF (2003–2019) (Accessed 2019.12.31.)

According to our statistical review, reports of contaminated DNP products have primarily been reported from the United Kingdom. Sibutramine was reported less frequently in other nations, with Germany having the largest number of reports, followed by Cyprus and Slovenia (**Annex 6**,**7** and **8**). According to the reports, DNP first appeared as an adulterant in Finland in 2003. There were no more reports on DNP until 2017, whereby it reappeared, and the production of DNP-containing products began to rise sharply. The notifications came from Cyprus and the United Kingdom. After its initial discovery in food supplements in 2005, sibutramine has become a widely used adulterant in the EU. The number of reports on supplements containing sibutramine peaked in 2012 (21 reports), which concerned many EU nations. The first two reports on phenolphthalein were from Cyprus and Hungary. Seven complaints of phenolphthalein were from Germany in 2013. Based on the records, the conclusion is that sibutramine emerged more often, but it occurred in less products. DNP was most abundant in 2018 (41 times) and 2019 (70 times), although sibutramine's popularity seems to peak in the early 2010s with 14 and 21 reports, respectively, were recorded in 2011 and 2012. In 2012, there were six complaints of phenolphthalein; in 2013, there were seven reports, which represented phenolphthalein in the highest amount. *Hoodia gordonii* (66 of 117, 56.4%), *Stevia rebaudiana* (23, 19.66%), and *Acacia rigidula* (28, 23.93%) were reported as illegal herbal products based on the RASFF signals. Poland, Lithuania, France, Malta, Spain, Belgium, Austria, Switzerland, Ireland, Sweden, and Finland were the nations impacted by contaminated herbal products (**Annex 9**,**10** and **11).** The first record of *Hoodia gordonii* was made in the Netherlands in 2005 (2 reports). The highest recorded number of *H. gordonii*-containing products (30 reports) was reported in 2017. There were no *Hoodia gordonii* reports in 2016. Denmark reported the first emergence of a product containing unauthorized *Stevia rebaudiana* in 2006. There were four reports of unapproved *Stevia rebaudiana*-containing products in 2010. From 1988 through 2019, it was present every year with the exception of 2005, 2015, 2018, and 2019. The first reports of *Acacia rigidula* were reported in 2016, initially in the Netherlands, but later also in Belgium, Austria, France, Malta, Spain, and other European nations. In total, 28 records were recorded in RASFF. In 2017, there were 30 reports of *Hoodia gordonii*, which was present more frequently but in smaller amounts. Although unauthorized *Stevia rebaudiana* has been reported nearly every year, the maximum reports were only four. *Acacia rigidula* only began to appear in 2016, and

in 2017 it reappeared with 23 records. Overall, 53 (53 of 372 reports, 14.25%) reports, highest amount of 16 in 2016 and 15 in 2013 were recorded in connection with synephrine in "C" category. Notifications were originated from: Norway, Denmark, Poland, France, Sweden, Finland, Germany, and the Netherlands.[7] The first report of synephrine was in 2007. The second record was found in 2009 and the notifications were constantly emerged until the end of the analysed time interval, 2009-2019 (**Annex 9**, **10** and **11**).

5.2. Efficacy and safety of *Citrus aurantium* extracts and *p*-synephrine

5.2.1. Literature search

2,435 articles were found as a result of the literature search (**Annex 12**). After duplicates were removed, 1,472 papers remained, and 51 publications were revised and retrieved for full text screening (excluded: n=1,421). Eligibility was determined for the 51 full-text articles. Following revision, it was determined that 21 studies were suitable for qualitative analysis. Articles were disqualified if they were not peer-reviewed scientific papers (such as abstracts or posters) (n=2), if they were clinical trials without synephrine (n=3), if they were not human clinical studies (n=1), or if they did not specify the length of the experiment (n=5). Additional studies were excluded if they missed: relevant outcomes (n=4), statistical values (n=1), detailed outcomes (n=7), placebo-control (n=3), or were not clinical studies (n=4). The authors of two trials[196,197] did not specify the precise dosage of synephrine, and one research was open-label[198], causing these studies ineligible for further quantitative analyses. Consequently, the final quantitative analysis comprised a total of 18 studies involving 341 participants. In a two-way, crossover, open-label trial, *Penzak* et al. evaluated the cardiovascular effects of approximately 13–14 mg of synephrine, which had no significant impact on SBP, DBP, or HR in 12 healthy individuals.[198] A randomized crossover trial was conducted by *Kliszczewicz* et al. to compare the effects of 100 mg of *Citrus aurantium* (CA) powder (with unknown synephrine dosage) to 100 mg of caffeine or placebo. The HR of test subjects significantly increased in a time-dependent manner after ingesting *Citrus aurantium.*[196] In a separate randomized double-blind study, participants drank 140 mL of a high-energy beverage with unspecified amounts of methyl-synephrine.[197] According to their findings, the intervention group's SBP was significantly higher during the three-hour research period, but neither the HR nor the DBP underwent any significant changes.

5.2.2. Characteristics of the trials

All the included trials (n=18) were double-blinded, prospective, parallel or crossover, within-subjects, or counterbalanced studies (**Annex 13**). There were seven crossover trials[199-205]; five were parallel-designed[173,206-209]; four had within-subject designe[210,211] or other[212,213] designs and two was carried out in a counterbalanced manner.[214,215] Fourteen studies evaluated synephrine's acute effects.[199-205,209-215] The effects of longer treatment duration (ranging from 4 to 8 weeks) was evaluated in four trials.[173,206-208] The daily dose of synephrine ranged from 6 to 214 mg. The inclusion criteria of the trials varied from one study to another. Eight trials exclusively included participants who were physically active.[173,201,205,206,208,210,212,215] Healthy, normotensive, but untrained individuals took part in eight studies.[199,200,202,204,207,209,211,213] Overweight adults were enrolled in four trials.[173,203,208,214] Exercise training was a part of nine trials.[173,201,205,206,208,212-215] Weight loss and body compositions were assessed in three articles[173,206,208], and all of these trials required exercise intervention, and two involved dietary restrictions.[173,208] In nine trials workout interventions were not applied.[199,200,202-204,207,209-211] In seven studies, the primary evaluated intervention was not synephrine (e.g. caffeine).[173,200,201,203,206,208,214] Caffeine also speeds up the heartbeat and raises blood pressure which could change the outcome in the final analysis. In one study[212], it was mentioned that all participants consumed less than 50 mg of caffeine per day, the authors of the other studies did not state if the volunteers were regular or irregular caffeine users. Based on the average amount of caffeine consumed, *Bush* et al.[210] and *Ratamess* et al.[211] split the groups. However, in order to make the examined groups more homogeneous, the subgroup of habitual high caffeine users (>300 mg) was left out of our final meta-analysis. Caffeine restriction was requested in seven trials.[173,205,207,208,212,213,215]

5.2.3. Demography of the patients

The inclusion process was consistent with the Helsinki declaration in all trials, involving only adult patients (age above 18 years or older). Pregnant women were excluded in eight trials.[173,199-202,204,207,208] Smoking was a prohibited activity or only non-smokers took part in nine trials.[199,201,205,206,214,210-212,215] The age of the participants ranged from 18 to 51 years. Participants were either healthy with sedentary or active lifestyle, or overweight. Additionally, more male patients (68.45%) were randomly assigned. A total of 341 subjects

were examined with considering the crossover design and the within-subject design (**Annex 14**).

5.2.4. Outcomes

SBP, DBP, HR, weight loss, body fat percentage, fat mass, fat free mass, blood glucose, and RER values were the analysed outcomes. Other adverse events (e.g. complaints of headache[202], hyperventilation[214], racing heart-rate, feeling dizzy, and feeling irritable or perspiring[211], palpitations, shortness of breath, anxiousness, and blurred vision[206]) were also mentioned in several studies, but they were too heterogeneous to be statistically examined. In the included studies, increase in VO_2 uptake[201], an increase in energy expenditure[200], an increase in fat oxidation and a decrease in carbohydrate utilization[213,215], and other changes in the ratings of perceived exertion were also reported.[212,215] However, the these were left out of the final meta-analysis because none of them were reported in at least three articles or were based on too heterogeneous characteristics (time intervals) or lacked detailed results.

5.2.4.1. Cardiovascular outcomes

To evaluate the effects of synephrine on blood pressure, a total of 11 trials with 222 participants, 6 different time sets, and various dosages (range 10–214 mg) were used. The synephrine group's SBP tended to increase (**Figure 2**). The mean difference was 1.21 mmHg (95% CI: -2.57–5.00), which was not significant (p=0.53) but demonstrated a larger effect size for synephrine than for placebo 30–45 minutes after the administration of 20–50 mg synephrine. The post-post analysis revealed a non-significant increase in SBP (MD 1.56 mmHg, 95% CI: -1.11–4.24, p=0.25) following the administration of the products containing 49–214 mg synephrine for with an hour. Based on the results of to five studies including 61 patients, the effects of synephrine (49–180 mg) remained insignificant after two hours, (MD 3.89 mmHg, 95% CI: -0.99–8.77, p=0.12). Only a small effect on SBP was seen after 3 hours after administration (MD 0.34 mmHg, 95% CI: -2.18–2.87, p=0.79), and it diminished after 6–8 hours from consumption (MD 0.10 mmHg, 95% CI: -3.82–4.02, p=0.96; dosage 27–108 mg). Based on the results of two trials involving 75 patients, after 8 weeks of administration, a daily dose of 10–49 mg synephrine had a significant effect on the systolic blood pressure (MD 6.37 mmHg, 95% CI: 1.02–11.72, p=0.02).

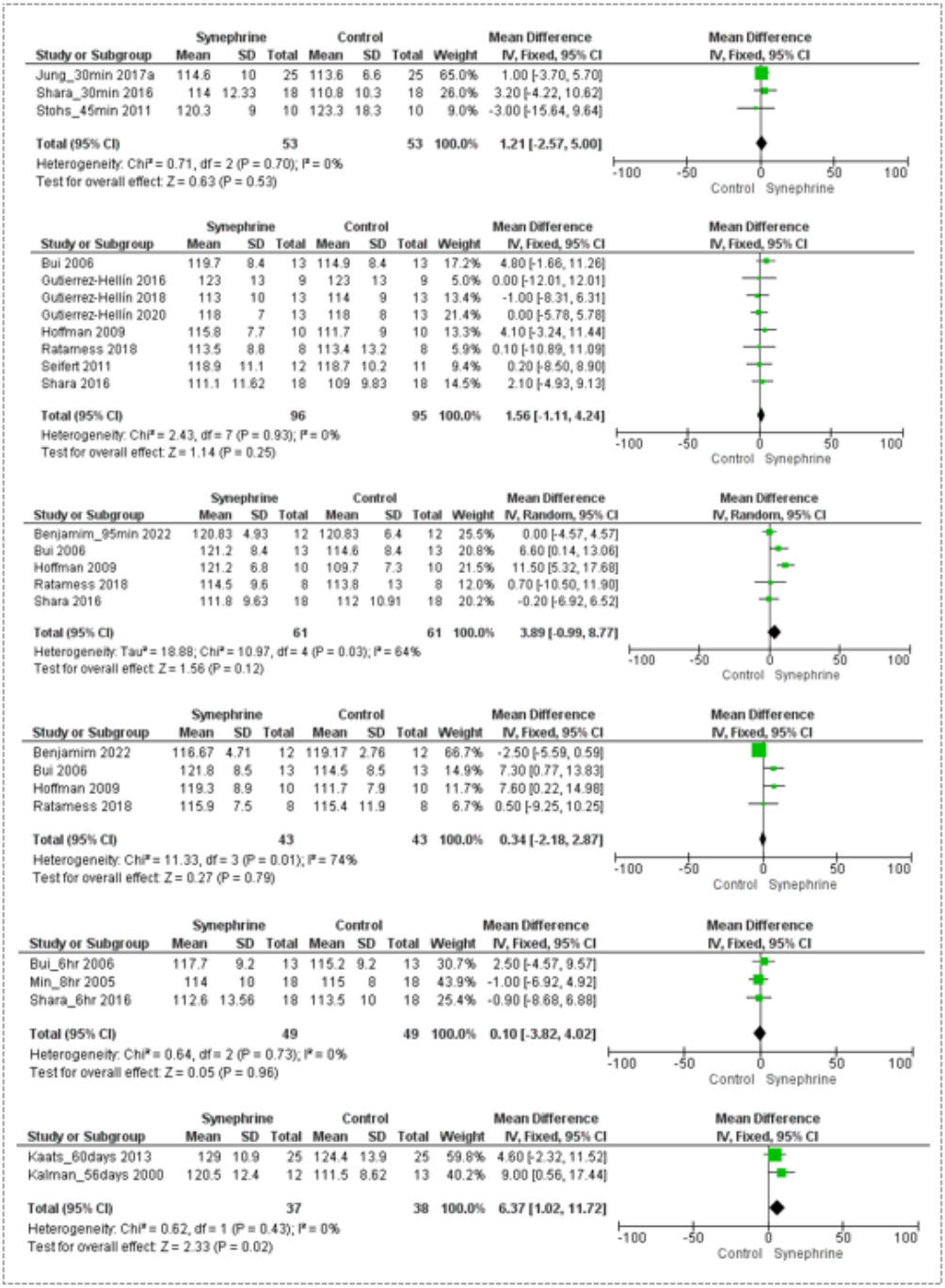


Figure 2. Forest plot diagram of synephrine on systolic blood pressure acutely (after 30–45 min, 1 h, 2 h, 3 h, and 6–8 h) and long duration (56–60 days) in the intervention and the control groups.

In DBP, the dosages and the articles that were included were identical; however, we took out one data point by two hours[205] because the statistical SD value "0" could not have been estimated from the original article. Synephrine (20–214 mg) administration did not significantly affect DBP neither 30–45 minutes after administration (MD -0.88 mmHg,

95%CI: -4.45–2.70, p=0.63), nor 1 hour after administration (MD -0.89 mmHg, 95%CI: -2.92–1.13, p=0.39), nor 2 hours after administration (MD 0.48 mmHg, 95%CI: -2.22–3.17, p=0.73); nor 3 hours after administration (MD 0.40 mmHg 95%CI: -1.83–2.62, p=0.73); nor 6–8 hours after administration (MD -0.43 mmHg 95%CI: -3.52–2.66, p=0.78). A significant effect on DBP was observed after long-term (8 weeks) use of synephrine (10–49 mg) (MD 4.33 mmHg, 95% CI: 0.48–8.18, p=0.03), based on two trials with 75 participants (**Figure 3**).

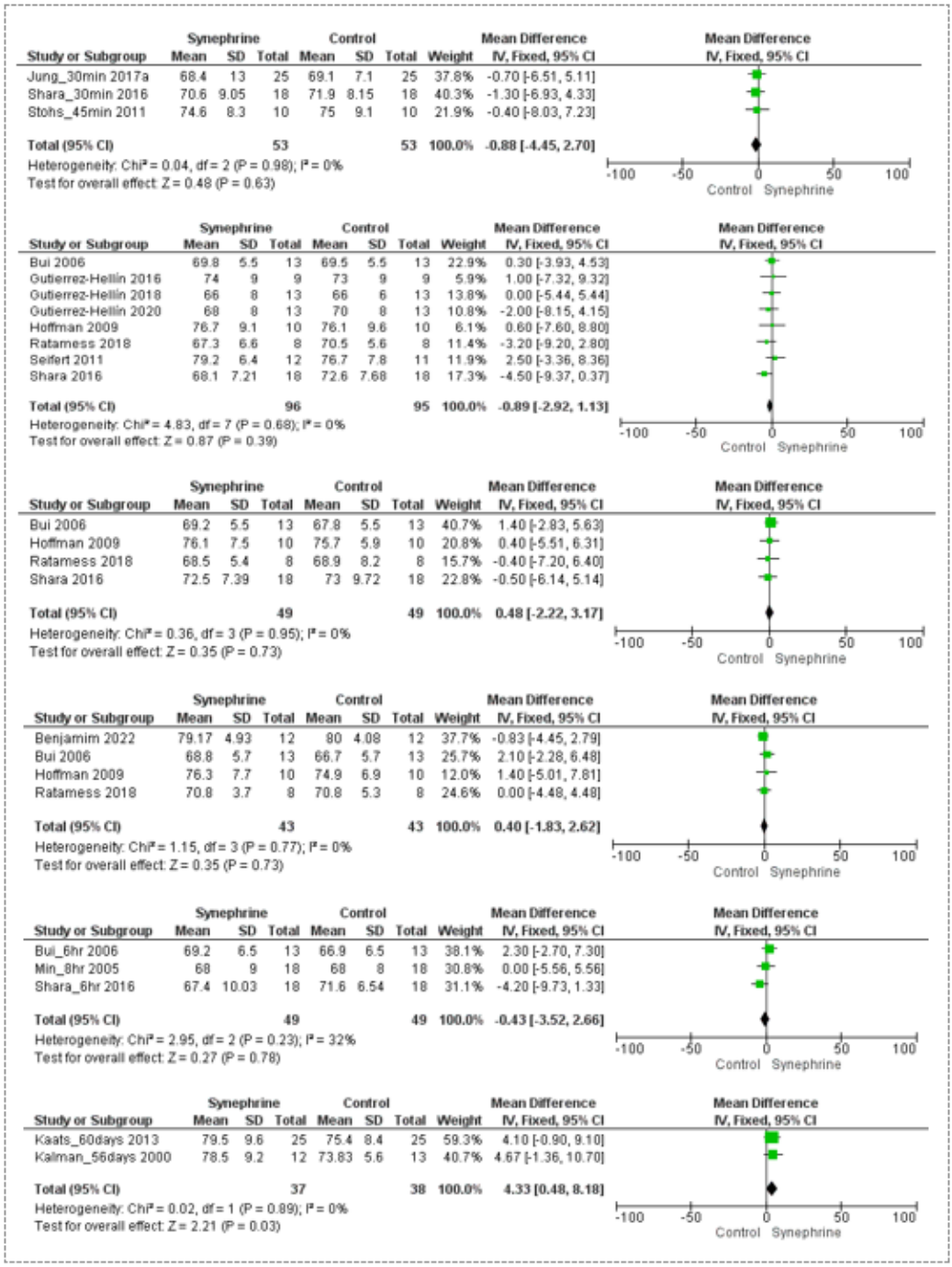


Figure 3. Forest plot diagram of synephrine on diastolic blood pressure acutely (after 30–45 min; 1 h; 2 h; 3 h; and 6–8 h) and long duration (56–60 days) in the intervention and the control groups.

Overall, the effects of synephrine on heart rate were investigated in 9 studies involving 129 participants, with 6 different time periods, and varying synephrine dosages (range 20–214 mg). Significant differences between synephrine and placebo were not detected; nevertheless, the heart rate in the synephrine group modestly rose 30 minutes to 6 hours after consumption (**Figure 4**). The mean difference in heart rate was 3.15 beats per minute (30–45 minutes) after taking 20–50 mg synephrine (95% CI: -0.41–6.71, p=0.08), and it was 1.11 beats per minute (95% CI: -1.32–3.53, p=0.37) after 1 hour of taking 49–214 mg synephrine. A non-significant increase in heart rate was seen 2 hours after ingesting 49–180 mg of synephrine (MD 3.15 beat/min, 95% CI: -0.65–6.96, p=0.10). Based on four studies involving 43 subjects, the synephrine-adjusted increase in heart rate was 3.48 beat/min (95% CI: -0.33–7.29, p=0.07) 3 hours after ingesting 60–180 mg of synephrine. Based on the included studies, the effects were still not significant after 4 hours (MD 3.25 beat/min, 95% CI: -2.86–9.35, p=0.30), or after 6 hours (MD 2.84 beat/min, 95% CI: -2.80–8.48, p=0.32; range 49–108 mg).

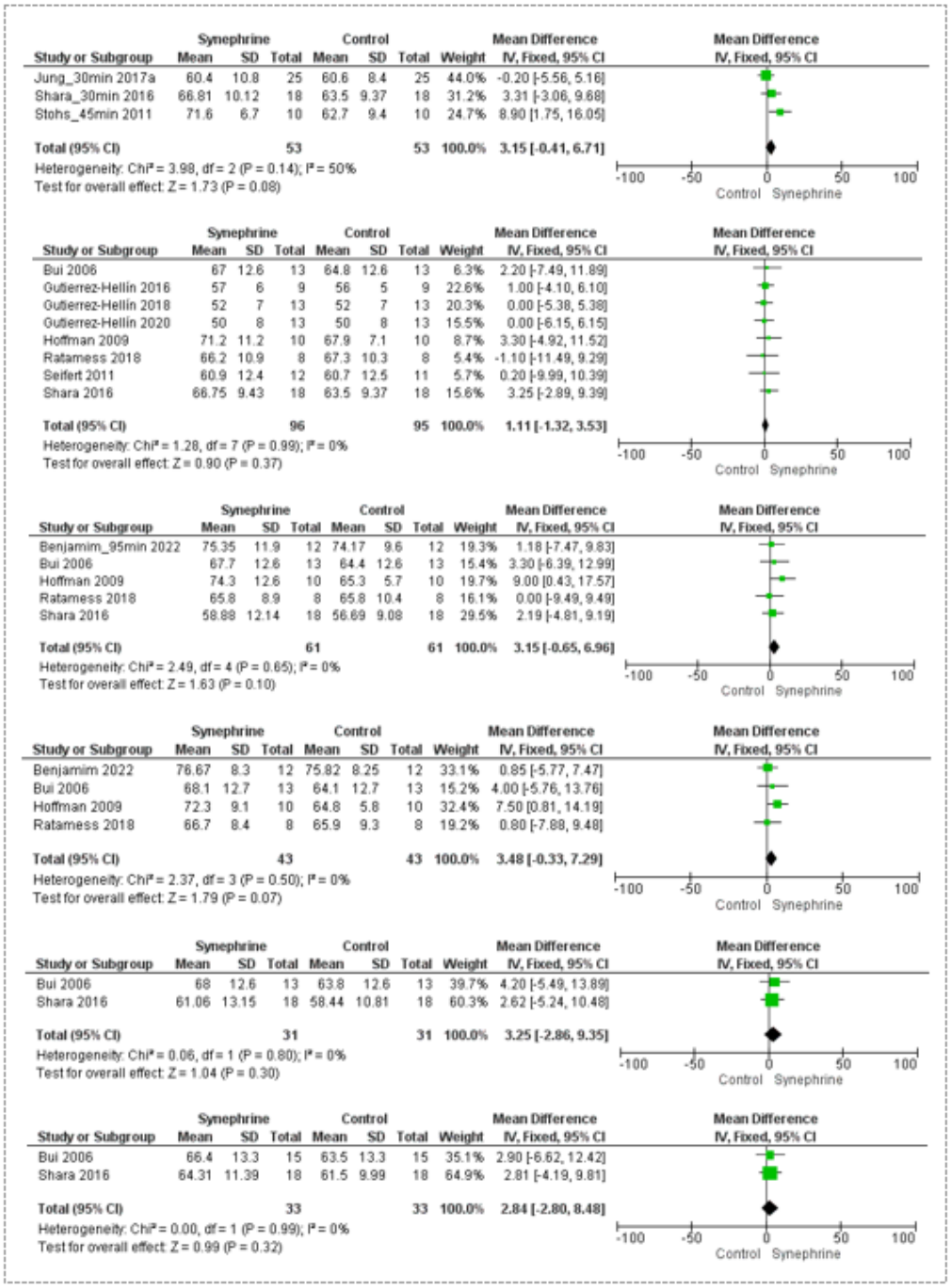
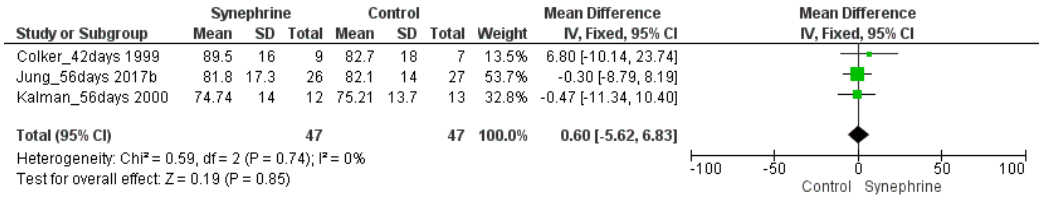


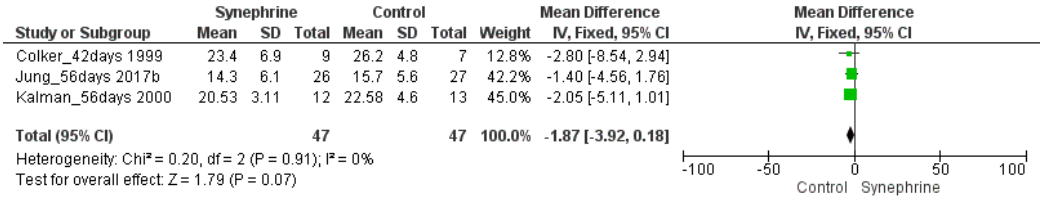
Figure 4. Forest plot diagram of synephrine on heart rate acutely (after 30–45 min, 1 h, 2 h, 3 h, 4 h, and 6 h) interval in the intervention and in the control groups.

5.2.4.2. Weight loss and body composition

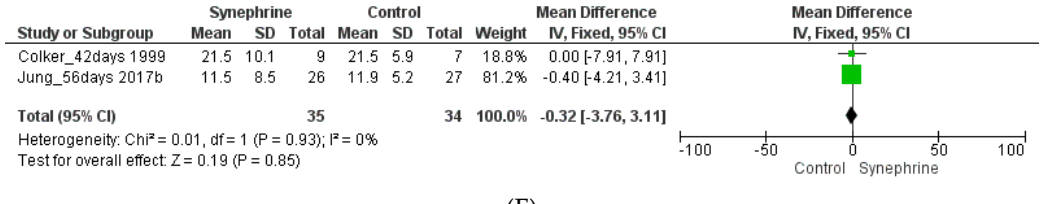
Three trials were analysed to determine the impact of synephrine on weight loss.[173,206,208] The daily doses of synephrine were 54 mg, 20 mg, and 10 (5 × 2) mg, respectively, the trials lasted for several weeks (42–56 days or 6–8 weeks). Our meta-analysis determined that its impact on weight loss was not statistically significant (MD 0.60 kg, 95% CI: -5.62–6.83, p=0.85) (**Figure 5D**). Only a slight reduction of the body fat was observed after synephrine ingestion (MD -1.87%, 95% CI: -3.92–0.18, p=0.07), and the impact was statistically not different from that of placebo (**Figure 5E**). Synephrine (20 or 54 mg) treatment had no significant effects on fat mass. The average difference was -0.32 kg (95% CI: -3.76–3.11, p=0.85) (**Figure 5F**). Based on the included studies, low doses of synephrine (10 and 20 mg) did not significantly alter the fat free mass (MD 0.47 kg, 95% CI: -4.19–5.13, p=0.84) (**Figure 5G**).



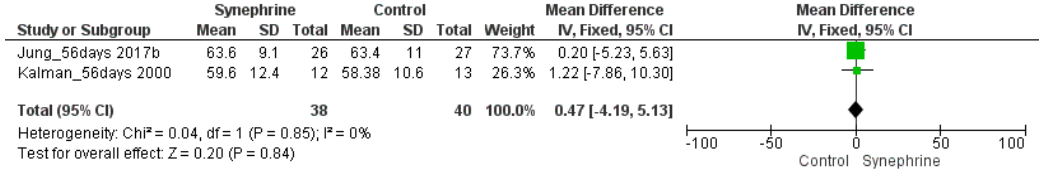
(D)



(E)



(F)



(G)

Figure 5. Forest plot diagram of synephrine on weight (D), body fat (E), fat mass (F), and fat free mass (G) after 42–56 days (6–8 weeks) in the intervention and in the control groups.

5.2.4.3. Other outcomes

Based on the included studies, 6–103 mg synephrine did not significantly affect blood glucose levels. After 2–3 hours of the consumption of synephrine, blood glucose levels increased slightly but not significantly (MD 4.62 mg/dL, 95% CI: -3.04–12.29, p=0.24) with moderate heterogeneity (TAU^2=30.32%) (**Figure 6 and Annex 15**). The effect of synephrine on blood and plasma glucose was likewise not significant in the head-to-head studies.[201,210,214]

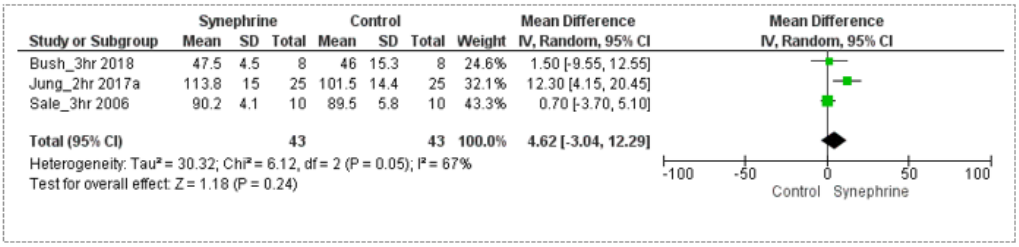


Figure 6. Forest plot diagram of synephrine's acute effects on blood glucose in the intervention and in the control groups (2–3 hours).

Three studies were conducted to examine the acute effects of synephrine (6–60 mg) on respiratory exchange ratio (RER).[200,203,214] After 1, 2, or 3 hours of dosing, synephrine had no significant effects. After one hour of consumption, there was no difference [the mean difference was 0.00 (95% CI: -0.03–0.03, p=0.91)]; strengthened by a non-classical leave one out analysis; after two hours, synephrine produced a difference of -0.02 (95% CI: -0.12–0.09, p=0.75; after three hours, a difference of -0.02 (95% CI: -0.12–0.08, p=0.73) was observed (**Annex 16**).

5.2.5. Risk of bias

Overall, we rated the methodological quality of the trials included in our final quantitative analysis to be satisfactory, with the majority of the studies having low or unclear risk of bias (**Annex 4 and 5**). Three studies provided descriptions of the random sequence generation[199,204,205] and the measures used to ensure allocation concealment were revealed in eight trials.[199,201,205,206,210,211,213,215] As a result, these studies' selection bias (i.e. random sequence generation or allocation concealment) was considered to be low. *Sale* et al.,[214] on the other hand, did not specify whether or not their study was randomised, hence there was a high possibility of selection bias. The remaining studies lacked the necessary data to assess

selection bias, hence it these studies had an unclear risk of selection bias. Four studies[199,205,206,215] were judged to have low risk of performance bias, whereas 14 studies were considered to have unclear risk of performance bias because it was unclear whether the treatment and the comparator were identical in size, shape, colour, and odour and it was also unclear who and until when was blinded. Four studies[199,202,212,213] had low risk of detection bias; however, it was not obvious from the remaining 14 studies whether the data were evaluated in a blinded manner or not. All the included studies had low risk of attrition and reporting bias. Since five trials were at least partially funded by pharmaceutical companies with relations to the products being evaluated, these studies reckoned to have uncertain risk of other bias.[204,209-211,214]

6. DISCUSSION

Our research focused on products with an intended use as a slimming agent. Firstly, we summarized the trends of illegal food supplements related with warning signals in RASFF between 1988 and 2019. The products reported for suspected quality issues (e.g. adulteration) are potential sources of serious risks. Hence, these products may cause serious adverse effects and dangerous interactions in sensitive patients.[190-193] We collected and summarized the most frequently used unauthorized natural and synthetic adulterants and assessed the trends of adulterated and illegal food supplements based on the warnings of the RASFF. This work was designed to help risk management and risk minimization concerning food supplements.

The rising frequency of illegal food supplement signals in RASFF is alarming. Between 1988 and 2019, DNP and sibutramine were the most frequent illegal substances in weight loss products. The former may cause rapid weight loss, but serious side effects are related to its use.[65] In the past, numerous deaths linked to DNP have been reported.[216] DNP was identified as an adulterant for the first time in 2003, however between 2017 and 2019, more products containing this compound have been reported. Products with DNP-contamination were primarily found in the United Kingdom. Although sibutramine was reported from several countries, there were fewer products that included it. Based on the SCOUT trial, sibutramine increases the risk of nonfatal myocardial infarction and nonfatal stroke in individuals with pre-existing cardiovascular disease and increases the likelihood of high blood pressure or rapid heartbeat.[77]

It is alarming, that a large percentage of the reported signals were associated with hazardous synthetic drugs like DNP, sibutramine and phenolphthalein. DNP has been the subject of an increasing number of reports, and as in the medical literature, the lethal oral dose is about only 1–3 g per os, and 3 g has proven fatal, even in divided doses over a period of 5 days.[217] Although the dosages from the fatal reports vary from 300 mg to 10 g, there is no safe level of DNP.[218] Therefore, DNP should be monitored more closely in the future. As the notifications accessed in the RASFF system did not contain the dosage of DNP in the offered food supplements, it must be taken even more seriously as the majority (99%) of the reports were in serious risk category.

Among the most popular food supplements of natural origin, extracts of *Hoodia gordonii*, *Stevia rebaudiana* and *Vachellia rigidula* were the most frequently registered illegal items in RASFF from 1988 to 2019. Based on the results of our research of RASFF, *Stevia rebaudiana* appears to be the least harmful and least risky ingredient and it was reported in a modest amount. Even though it has been used as a traditional medicine for hundreds of years, additional scientific and clinical research is still required to confirm its safety because it was almost consistently represented in RASFF from 1988 to 2017 and is extremely popular by customers.[2] The safety of the other two plants (*H. gordonii* and *A. rigidula*) has not been established scientifically, and they are still not accepted as novel foods.[145,158] Despite the fact that *H. gordonii* is frequently used as an adulterant and promoted for its ability to aid weight loss, little is understood about its chemical components and their action mechanism. Recent studies revealed that taking *H. gordonii* may raise blood pressure and heart rate.[145] *H. gordonii* has been resurfacing often since 1988, it is obligatory to monitor food supplements that include *Hoodia*. Several biogenic amines can be found in the native shrub *A. rigidula*, which grows in the South-eastern United States. The plant has been utilized for weight loss products, but neither its traditional use – it has never been applied in traditional medicine – nor the literature data have yet provided evidence of its effects. Recent occurrence of *Acacia rigidula* in the RASFF portal emphasizes the need to monitor *A. rigidula* in dietary supplements. Because of there is no legal regulation that limits the amount of synephrine and other alkaloids in dietary supplements, it would be desirable that each country set a maximum quantity of synephrine.[180,181]

Because synephrine has a daily dose limit in some countries, there have been constant reports (n=53) in the RASFF about products containing more synephrine than allowed. Although its efficacy and safety have not been fully demonstrated,[161] *p*-synephrine, a protoalkaloid isolated from the immature fruit or peel of the bitter orange (*Citrus* x *aurantium*), is extensively utilized in weight reduction and sports performance products.[160] We aimed to determine the efficacy and safety of synephrine in order to dispel myths surrounding its use because it appears that legal background and notification procedures do not always guarantee safety and frequently lack scientific evidence to ensure efficacy. Synephrine is frequently mentioned in RASFF in connection with UL issues. Our systematic review and meta-analysis revealed that *p*-synephrine had no effects on body weight or composition measures, it did raise blood

pressure over time. This meta-analysis examined 341 adult participants from 18 trials in total. To evaluate synephrine's effects on weight loss and determine its safety based on its effects on cardiovascular variables, different time sets had to be applied depending on the original time points in each outcome. According to the literature, the range of daily doses for *p*-synephrine is 25 to 100 mg,[167,219,220] but participants in the included trials took 6-214 mg daily. According to our meta-analysis, synephrine significantly elevated systolic blood pressure when taking for prolonged time, but it did not have such effects acutely (p=0.02). When used for extended periods of time (8 weeks), it demonstrated similar significant effects and less pronounced acute effects on diastolic blood pressure (p=0.03). The heart rate increased following acute synephrine administration, although the difference remained insignificant; the biggest elevation was detected 3 hours after ingestion (p=0.07). Our investigation led to the conclusion that prolonged use of synephrine resulted a not significant change [mean difference of 0.6 kg (p=0.85)] in body weight. Body fat (-1.87%, n=94, p=0.07), fat mass (-0.32 kg, n=69, p=0.85), and fat free mass (0.47 kg, n=78, p=0.84) were all similarly unaffected by synephrine. According to some research, *p*-synephrine may be able to regulate blood sugar levels by encouraging the uptake of extra blood sugar through either insulin-dependent or -independent pathways in skeletal muscles.[221] Maintaining appropriate blood glucose levels would be advantageous, indicating a higher hepatic glucose release, which would be beneficial during exercise.[201,222] However, based on our findings, taking synephrine acutely did not significantly change blood glucose levels (p=0.24), and taking 6-103 mg synephrine did not have an impact on blood glucose maintenance. Our findings imply that taking 6–60 mg of synephrine does not significantly alter RER values. 33 participants were examined over 3 articles in our analysis. In these studies, the effects of synephrine were evaluated an hour after consumption. Approximately 2–3 hours after intake, only data of 20 subjects were accessible. Since all three of the evaluated trials included a supplement that contained extra caffeine, RER value alterations in the studies were likely caused by caffeine.[203] Lower RER levels reflect lipid oxidation, while higher RER values suggest that carbohydrates are being used as fuel primarily.[223,224] In response to equivalent workloads, physically active and trained subjects show lower RER values than untrained sedentary subjects.[225-227]

Our results clearly indicate that the use of synephrine may negatively affect cardiovascular health. The use of ephedrine is linked to an elevated risk of cardiovascular morbidity and mortality, a comparably potent but more secure substitute would be greatly appreciated.[189,162] The dosage of synephrine employed in the analysis of weight loss was daily 10–54 mg for 42–56 days, which is almost the same as the dosage that caused a cardiovascular adverse event (increased blood pressure) 56–60 days following the administration of 10–49 mg synephrine. Our meta-analysis showed that using synephrine also hinders the cardiovascular health; therefore, it might not be a safe substitute for ephedrine for people who have pre-existing comorbidities. Products containing *p*-synephrine are promoted to people who desire to utilize more energy during low- to moderate-intensity activity.[161] However, it has not yet been demonstrated that consuming bitter orange or synephrine can reduce body fat or increase weight loss.[161] The fact that only information from peer-reviewed publications was included and that all the included studies were double blinded are major strength of our meta-analysis. However, the analysis has a number of limitations. First of all, the investigated products varied in terms of their composition and contained different dosages (ranging from 6–214 mg) of synephrine. In one study, *m*- and *p*- synephrine were both used[202] and one study investigated the effects of methyl-synephrine HCl.[200] Overall six trials used isolated *p*-synephrine.[209-213,215] The remaining ten investigations used products (e.g. bitter orange extracts[199,204,205] or other formulations[173,200,201,203,206,208,214]) that were standardized to synephrine. High attrition and the fact that just a few studies evaluated the same outcomes resulting in very short plots were the main limitations of this meta-analysis. On the other hand, respondents displayed a wide range of characteristics related to age and physical activity, and more males were examined. Exercise intervention was used in certain trials, which further exacerbated the data's heterogeneity. Prior to this study, *Stohs* et al. conducted a thorough systematic review of synephrine; however, no statistical analyses were done.[228]

7. CONCLUSIONS

Given the ongoing global expansion of the food supplement sector, it is critical to understand the potential for counterfeit products to pose a public health risk. Counterfeit signals are important tools to make food supplements safer for the consumers, and the protect their health. It is necessary to establish a number of initiatives to reduce the prevalence of counterfeit products by strengthening industry standards for testing, efficacy, and safety. On the other hand, there is an obvious need for efficient solutions to help weight loss because currently there are only a few accessible treatment choices.

Unpredictable interactions between easily available counterfeited food supplements and other medications can also lead to significant adverse events. It is concerning that it seems that there are increasing numbers of signals in RASFF about contaminated products. The RASFF contained overall 372 records for weight loss food supplements with a quality concern between 1988 and 2019. 319 (85.75%) contained unauthorized ingredients such as DNP [113 of 319 (35.4%)] and sibutramine (69, 21.6%). There were less reports of unauthorized herbal substances [117/319 (36.68%)]. In the category of inappropriate dosages, synephrine was identified 53 [53/372 (14.25%)] times, as the synephrine content in these products was often over the authorized level in some countries.

Based on our observations synephrine cannot be considered as a safe and effective alternative for *Ephedra sinica* Stapf or ephedrine in the dose range of 10–214 mg. Furthermore, our meta-analysis identified safety issues with synephrine consumption. When used for longer periods of time, *p*-synephrine significantly raised both systolic and diastolic blood pressure and it also tended to elevate heart rate and systolic blood pressure acutely. Our meta-analysis revealed that it had no beneficial effects on body composition or weight loss. Consequently, the cost/benefit ratio of its use is unfavourable. The regulatory authorities, the industry and consumers must re-evaluate their perspectives on the balance between product quality and efficacy regarding food supplements as the current legal situation does not prevent all potentially dangerous weight loss substances from entering the market. My thesis only touches on a small portion of the vast and intricate problem of counterfeit food supplements.

8. REFERENCES

1. World Health Organization. *Data and statistics- the challenge of obesity*. Geneva, Switzerland:World Health Organization. (World Health Organization, 2019).
2. Srivastava, G. & Apovian, C. M. Current pharmacotherapy for obesity. *Nat. Rev. Endocrinol.* **14**, 12–24 (2018).
3. Onakpoya, I. J., Heneghan, C. J. & Aronson, J. K. Post-marketing withdrawal of anti-obesity medicinal products because of adverse drug reactions: a systematic review. *BMC Med.* **14**, 191 (2016).
4. Grand View Research. Market Analysis Report: Weight Loss Supplements Market Size, Share & Trends Analysis Report By End User (18-40 Years, Under 18 Years), By Distribution Channel (Offline, Online), By Type (Powders, Pills), By Ingredient, And Segment Forecasts, 2021 – 2028. Available at: https://www.grandviewresearch.com/industry-analysis/weight-loss-supplements-market-report (Accessed January 18, 2023).
5. Koncz, D., Tóth, B., Roza, O. & Csupor, D. A Systematic Review of the European Rapid Alert System for Food and Feed: Tendencies in Illegal Food Supplements for Weight Loss. *Front. Pharmacol.* **11**, 1–14 (2021).
6. Van Breemen, R. B., Fong, H. H. S. & Farnsworth, N. R. Ensuring the safety of botanical dietary supplements. *Am. J. Clin. Nutr.* **87**, 509–513 (2008).
7. Rapid Alert System for Food and Feed (RASFF). Available at: https://ec.europa.eu/food/safety/rasff/how_does_rasff_work/legal_basis (2020) (Accessed October 13, 2020).
8. Loos, R. J. F. & Yeo, G. S. H. The genetics of obesity: from discovery to biology. *Nat. Rev. Genet.* **23**, 120–133 (2022).
9. Finucane, M. M. *et al.* National, regional, and global trends in body-mass index since 1980: Systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. *Lancet* **377**, 557–567 (2011).
10. World Health Organization. *Obesity and overweight*. Geneva, Switzerland: World Health Organization (World Health Organization, 2018).
11. Montan, P. D. *et al.* Pharmacologic therapy of obesity: mechanisms of action and cardiometabolic effects. *Ann. Transl. Med.* **7**, 393–393 (2019).
12. Kopelman, P.G. Obesity as a medical problem. *Nature* **404**, 635–643 (2000).
13. Meldrum, D. R., Morris, M. A. & Gambone, J. C. Obesity pandemic: causes, consequences, and solutions—but do we have the will? *Fertil. Steril.* **107**, 833–839 (2017).
14. Reuter, C. P. *et al.* Associação entre sobrepeso e obesidade em escolares com o polimorfismo rs9939609 (FTO) e histórico familiar de obesidade. *J. Pediatr. (Rio. J).* **92**, 493–498 (2016).
15. Corica, D. *et al.* Does Family History of Obesity, Cardiovascular, and Metabolic Diseases Influence Onset and Severity of Childhood Obesity? *Front. Endocrinol. (Lausanne).* **9**, (2018).
16. Wu, Y. *et al.* Genetics of obesity traits: a bivariate genome-wide association analysis. *Front. Genet.* **9**, 179 (2018).
17. Lin, X. & Li, H. Obesity: Epidemiology, Pathophysiology, and Therapeutics. *Front. Endocrinol. (Lausanne).* **12**, (2021).
18. Zhi, C. *et al.* Connection between gut microbiome and the development of obesity. *Eur. J. Clin. Microbiol. Infect. Dis.* **38**, 1987–1998 (2019).
19. Moreno-Indias, I., Cardona, F., Tinahones, F. J. & Queipo-Ortuño, M. I. Impact of the gut microbiota on the development of obesity and type 2 diabetes mellitus. *Front. Microbiol.* **5**, 190 (2014).
20. Stunkard, A. J. & Wadden, T. A. Psychological aspects of severe obesity. *Am. J. Clin. Nutr.* **55**, 524S-532S (1992).
21. de Wit, L. *et al.* Depression and obesity: A meta-analysis of community-based studies. *Psychiatry Res.* **178**, 230–235 (2010).
22. DeFronzo, R. A. *et al.* Type 2 diabetes mellitus. *Nat. Rev. Dis. Prim.* **1**, 15019 (2015).
23. Kelly, T., Yang, W., Chen, C.-S., Reynolds, K. & He, J. Global burden of obesity in 2005 and projections to 2030. *Int. J. Obes.* **32**, 1431–1437 (2008).
24. Curioni, C. C. & Lourenço, P. M. Long-term weight loss after diet and exercise: a systematic review. *Int. J. Obes. (Lond).* **29**, 1168–1174 (2005).
25. Tonstad, S., Rössner, S., Rissanen, A. & Astrup, A. Medical management of obesity in Scandinavia

2016. *Obes. Med.* **1**, 38–44 (2016).
26. European Medicines Agency. Medicines. Available at: https://www.ema.europa.eu/en/medicines (2020) (Accessed October 15, 2022).
27. The State Institute for Drug Control (SUKL) Czech Republic Available at: http://www.sukl.eu/ (2022). (Accessed October 10, 2022).
28. Committee for Medicinal Products for Human Use (CHMP). Questions and answers on the review of orlistat-containing medicines Why was orlistat reviewed? Avilable at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Orlistat_31/WC500122883.pdf (Accessed January 18, 2023).
29. Lunagariya, N. A., Patel, N. K., Jagtap, S. C. & Bhutani, K. K. Inhibitors of pancreatic lipase: state of the art and clinical perspectives. *EXCLI J.* **13**, 897–921 (2014).
30. Al-Suwailem, A., Al-Tamimi, A., Al-Omar, M. & Al-Suhibani, M. Safety and Mechanism of Action of Orlistat (Tetrahydrolipstatin) as the First Local Antiobesity Drug. *J. Appl. Sci. Res.* **2**, 205–208 (2006).
31. Filippatos, T. *et al.* Orlistat-Associated Adverse Effects and Drug Interactions. *Drug Saf.* **31**, 53–65 (2008).
32. Halpern, B. & Mancini, M. C. Safety assessment of combination therapies in the treatment of obesity: focus on naltrexone/bupropion extended release and phentermine-topiramate extended release. *Expert Opin. Drug Saf.* **16**, 27–39 (2017).
33. Grossman, H. C., Hadjimarkou, M. M., Silva, R. M., Giraudo, S. Q. & Bodnar, R. J. Interrelationships between μ opioid and melanocortin receptors in mediating food intake in rats. *Brain Res.* **991**, 240–244 (2003).
34. Greenway, F. L. *et al.* Comparison of combined bupropion and naltrexone therapy for obesity with monotherapy and placebo. *J. Clin. Endocrinol. Metab.* **94**, 4898–4906 (2009).
35. Cone, R. D. Anatomy and regulation of the central melanocortin system. *Nat. Neurosci.* **8**, 571–578 (2005).
36. Caixàs, A., Albert, L., Capel, I. & Rigla, M. Naltrexone sustained-release/bupropion sustained-release for the management of obesity: review of the data to date. *Drug Des. Devel. Ther.* **8**, 1419–1427 (2014).
37. Sherman, M. M., Ungureanu, S. & Rey, J. A. Naltrexone/Bupropion ER (Contrave): Newly Approved Treatment Option for Chronic Weight Management in Obese Adults. *P T* **41**, 164–172 (2016).
38. Tek, C. Naltrexone HCI/bupropion HCI for chronic weight management in obese adults: patient selection and perspectives. *Patient Prefer. Adherence* **10**, 751–759 (2016).
39. James, W. P. T. *et al.* Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. *N. Engl. J. Med.* **363**, 905–917 (2010).
40. Connolly, H. M. *et al.* Valvular heart disease associated with fenfluramine-phentermine. *N. Engl. J. Med.* **337**, 581–588 (1997).
41. Vorsanger, M. H. *et al.* Cardiovascular Effects of the New Weight Loss Agents. *J. Am. Coll. Cardiol.* **68**, 849–859 (2016).
42. Narayanaswami, V. & Dwoskin, L. P. Obesity: Current and potential pharmacotherapeutics and targets. *Pharmacol. Ther.* **170**, 116–147 (2017).
43. Colman, E. Anorectics on trial: a half century of federal regulation of prescription appetite suppressants. *Ann. Intern. Med.* **143**, 380–385 (2005).
44. Shin, J. H. & Gadde, K. M. Clinical utility of phentermine/topiramate (Qsymia™) combination for the treatment of obesity. *Diabetes, Metab. Syndr. Obes. Targets Ther.* **6**, 131–139 (2013).
45. Collins, L. & Costello, R. A. *Glucagon-like Peptide-1 Receptor Agonists*. (StatPearls Publishing, Treasure Island (FL), (2019).
46. Marso, S. P. *et al.* Liraglutide and cardiovascular outcomes in type 2 diabetes. *N. Engl. J. Med.* **375**, 311–322 (2016).
47. Neff, L. M. & Kushner, R. F. Emerging role of GLP-1 receptor agonists in the treatment of obesity. *Diabetes. Metab. Syndr. Obes.* **3**, 263–273 (2010).
48. Mehta, A., Marso, S. P. & Neeland, I. J. Liraglutide for weight management: a critical review of the evidence. *Obes. Sci. Pract.* **3**, 3–14 (2017).
49. Christou, G. A., Katsiki, N. & Kiortsis, D. N. The Current Role of Liraglutide in the Pharmacotherapy of Obesity. *Curr. Vasc. Pharmacol.* **14**, 201–207 (2016).
50. Gomez-Peralta, F. & Abreu, C. Profile of semaglutide in the management of type 2 diabetes: Design, development, and place in therapy. *Drug Des. Devel. Ther.* **13**, 731–738 (2019).
51. Christou, G. A., Katsiki, N., Blundell, J., Fruhbeck, G. & Kiortsis, D. N. Semaglutide as a promising

antiobesity drug. *Obes. Rev.* **20**, 805–815 (2019).
52. Davies, M. *et al.* Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. *Lancet* **397**, 971–984 (2021).
53. Chao, A. M., Tronieri, J. S., Amaro, A. & Wadden, T. A. Semaglutide for the treatment of obesity. *Trends Cardiovasc. Med.* (2021).
54. Avgerinos, I. *et al.* Oral semaglutide for type 2 diabetes: A systematic review and meta-analysis. *Diabetes. Obes. Metab.* **22**, 335–345 (2020).
55. Bray, G. A. & Greenway, F. L. Current and potential drugs for treatment of obesity. *Endocr. Rev.* **20**, 805–875 (1999).
56. Bray, G. A. Use and abuse of appetite-suppressant drugs in the treatment of obesity. *Ann. Intern. Med.* **119**, 707–713 (1993).
57. Bazmi, E., Mousavi, F., Giahchin, L., Mokhtari, T. & Behnoush, B. Cardiovascular Complications of Acute Amphetamine Abuse: Cross-sectional study. *Sultan Qaboos Univ. Med. J.* **17**, e31–e37 (2017).
58. Kernan, W. N. *et al.* Phenylpropanolamine and the Risk of Hemorrhagic Stroke. *N. Engl. J. Med.* **343**, 1826–1832 (2000).
59. Walker, R. B., Fitz, L. D., Williams, L. M. & McDaniel, Y. M. The effect on ephedrine prodrugs on locomotor activity in rats. *Gen. Pharmacol.* **27**, 109–111 (1996).
60. Wellman, P. J. & Sellers, T. L. Weight loss induced by chronic phenylpropanolamine: Anorexia and brown adipose tissue thermogenesis. *Pharmacol. Biochem. Behav.* **24**, 605–611 (1986).
61. Tainter, M. L., Stockton, A. B. & Cutting, W. C. Use of dinitrophenol in obesity and related conditions: A Progress Report. *J. Am. Med. Assoc.* **101**, 1472–1475 (1933).
62. Cutting, W. C., Mehrtens, H. G. & Tainter, M. L. Actions And Uses of dinitrophenol: promising metabolic applications. *J. Am. Med. Assoc.* **101**, 193–195 (1933).
63. Tainter, M. L., Cutting, W. C. & Stockton, A. B. Use of Dinitrophenol in Nutritional Disorders. *Am. J. Public Heal. Nations Heal.* **24**, 1045–1053 (1934).
64. McFee, R. B., Caraccio, T. R., McGuigan, M. A., Reynolds, S. A. & Bellanger, P. Dying to be thin: a dinitrophenol related fatality. *Vet. Hum. Toxicol.* **46**, 251–254 (2004).
65. Colman, E. Dinitrophenol and obesity: an early twentieth-century regulatory dilemma. *Regul. Toxicol. Pharmacol.* **48**, 115–117 (2007).
66. Tainter, M. L., Cutting, W. C. & Hines, E. Effects of moderate doses of dininitrophenol on the energy exchange and nitrogen metabolism of patients under conditions of restricted dietary. *J. Pharmacol. Exp. Ther.* **55**, 326–353 (1935).
67. Porter, R. H. P. *et al.* Functional characterization of agonists at recombinant human 5-HT(2A), 5-HT(2B) and 5-HT(2C) receptors in CHO-K1 cells. *Br. J. Pharmacol.* **128**, 13–20 (1999).
68. Fitzgerald, L. W. *et al.* Possible role of valvular serotonin 5-HT(2B) receptors in the cardiopathy associated with fenfluramine. *Mol. Pharmacol.* **57**, 75–81 (2000).
69. Weintraub, M. *et al.* Long-term weight control study. I (weeks 0 to 34). The enhancement of behavior modification, caloric restriction, and exercise by fenfluramine plus phentermine versus placebo. *Clin. Pharmacol. Ther.* **51**, 586–594 (1992).
70. Abenhaim, L. *et al.* Appetite-suppressant drugs and the risk of primary pulmonary hypertension. International Primary Pulmonary Hypertension Study Group. *N. Engl. J. Med.* **335**, 609–616 (1996).
71. Wadden, T. A. *et al.* The Fen-Phen finale: A study of weight loss and valvular heart disease. *Obes. Res.* **6**, 278–284 (1998).
72. European Medicines Agency. The European agency for the evaluation of medicinal products (EMEA) patients' working group. *React. Wkly. NA.* 2, 2.
73. Rinaldi-Carmona, M. *et al.* Biochemical and pharmacological characterisation OF SR141716A, the first potent and selective brain cannabinoid receptor antagonist. *Life Sci.* **56**, 1941–1947 (1995).
74. Christensen, R., Kristensen, P. K., Bartels, E. M., Bliddal, H. & Astrup, A. Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials. *Lancet (London, England)* **370**, 1706–1713 (2007).
75. Sam, A. H., Salem, V. & Ghatei, M. A. Rimonabant: From RIO to Ban. *J. Obes.* **2011**, 432607 (2011).
76. McNeely, W. & Goa, K. L. Sibutramine. A review of its contribution to the management of obesity. *Drugs* **56**, 1093–1124 (1998).
77. Sharma, A. M. *et al.* Blood pressure changes associated with sibutramine and weight management - an analysis from the 6-week lead-in period of the sibutramine cardiovascular outcomes trial (SCOUT).

Diabetes. Obes. Metab. **11**, 239–250 (2009).
78. James, W. P. T. The SCOUT study: Risk-benefit profile of sibutramine in overweight high-risk cardiovascular patients. *Eur. Hear. Journal, Suppl.* **7**, 44–48 (2005).
79. Williams, G. Withdrawal of sibutramine in Europe. *BMJ (Clinical research ed.)* vol. 340 c824 (2010).
80. Ioannides-Demos, L. L., Proietto, J. & McNeil, J. J. Pharmacotherapy for Obesity. *Drugs* **65**, 1391–1418 (2005).
81. Smith, S. R. *et al.* Multicenter, placebo-controlled trial of lorcaserin for weight management. *N. Engl. J. Med.* **363**, 245–256 (2010).
82. European Medicines Agency. Withdrawal of the marketing authorisation application for Belviq (lorcaserin). **44**, 1–2 (2013).
83. DiNicolantonio, J. J., Chatterjee, S., O'Keefe, J. H. & Meier, P. Lorcaserin for the treatment of obesity? A closer look at its side effects. *Open Hear.* **1**, 19–22 (2014).
84. Bethesda, M. Liver Tox. *Clinical and Research Information on Drug Induced Liver Injury [Internet]*. (2012). (Accessed May 6, 2020).
85. Wharton, S., Bonder, R., Jeffery, A. & Christensen, R. A. G. The safety and effectiveness of commonly-marketed natural supplements for weight loss in populations with obesity: A critical review of the literature from 2006 to 2016. *Crit. Rev. Food Sci. Nutr.* **60**, 1614–1630 (2020).
86. Barrea, L. *et al.* Nutritionist and obesity: brief overview on efficacy, safety, and drug interactions of the main weight-loss dietary supplements. *Int. J. Obes. Suppl.* **9**, 32–49 (2019).
87. Ríos-Hoyo, A. & Gutiérrez-Salmeán, G. New Dietary Supplements for Obesity: What We Currently Know. *Curr. Obes. Rep.* **5**, 262–270 (2016).
88. Koncz, D., Tóth, B., Bahar, M. A., Roza, O. & Csupor, D. The Safety and Efficacy of *Citrus aurantium* (Bitter Orange) Extracts and p-Synephrine: A Systematic Review and Meta-Analysis. *Nutrients* **14**, 4019 (2022).
89. Pokhis, K., Bitterlich, N., Cornelli, U. & Cassano, G. Efficacy of polyglucosamine for weight loss-confirmed in a randomized double-blind, placebo-controlled clinical investigation. *BMC Obes.* **2**, 1–8 (2015).
90. Moraru, C., Mincea, M. M., Frandes, M., Timar, B. & Ostafe, V. A meta-analysis on randomised controlled clinical trials evaluating the effect of the dietary supplement chitosan on weight loss, lipid parameters and blood pressure. *Med.* **54**, 1–15 (2018).
91. Waibel, K. H., Haney, B., Moore, M., Whisman, B. & Gomez, R. Safety of chitosan bandages in shellfish allergic patients. *Mil. Med.* **176**, 1153–1156 (2011).
92. Gallaher, C. M., Munion, J., Hesslink, R. J., Wise, J. & Gallaher, D. D. Cholesterol reduction by glucomannan and chitosan is mediated by changes in cholesterol absorption and bile acid and fat excretion in rats. *J. Nutr.* **130**, 2753–2759 (2000).
93. Huang, S.-S., Sung, S.-H. & Chiang, C.-E. Chitosan potentiation of warfarin effect. *Ann. Pharmacother.* **41**, 1912–1914 (2007).
94. Jull, A., Mhurchu, C., Bennett, D., Dunshea-Mooij, C. & Rodgers, A. Chitosan for overweight or obesity. *Cochrane Database Syst. Rev.* **16**, CD003892 (2008).
95. Xiao, C., Gao, S. & Zhang, L. Blend films from konjac glucomannan and sodium alginate solutions and their preservative effect. *J. Appl. Polym. Sci.* **77**, 617–626 (2000).
96. Sood, N., Baker, W. L. & Coleman, C. I. Effect of glucomannan on plasma lipid and glucose concentrations, body weight, and blood pressure: systematic review and meta-analysis. *Am. J. Clin. Nutr.* **88**, 1167–1175 (2008).
97. Zalewski, B. M. & Szajewska, H. Effect of glucomannan supplementation on body weight in overweight and obese children: Protocol of a randomised controlled trial. *BMJ Open* **5**, 1–5 (2015).
98. Keithley, J. & Swanson, B. Glucomannan and obesity: a critical review. *Altern. Ther. Health Med.* **11**, 30–34 (2005).
99. Zheng, J., Zheng, S., Feng, Q., Zhang, Q. & Xiao, X. Dietary capsaicin and its anti-obesity potency: from mechanism to clinical implications. *Biosci. Rep.* **37**, (2017).
100. Whiting, S., Derbyshire, E. J. & Tiwari, B. Could capsaicinoids help to support weight management? A systematic review and meta-analysis of energy intake data. *Appetite* **73**, 183–188 (2014).
101. Ludy, M.-J., Moore, G. E. & Mattes, R. D. The effects of capsaicin and capsiate on energy balance: critical review and meta-analyses of studies in humans. *Chem. Senses* **37**, 103–121 (2012).
102. Henry, C. J. & Emery, B. Effect of spiced food on metabolic rate. *Hum. Nutr. Clin. Nutr.* **40**, 165–168 (1986).

103. Yoshioka, M., St-Pierre, S., Suzuki, M. & Tremblay, A. Effects of red pepper added to high-fat and high-carbohydrate meals on energy metabolism and substrate utilization in Japanese women. *Br. J. Nutr.* **80**, 503–510 (1998).
104. Lejeune, M. P. G. M., Kovacs, E. M. R. & Westerterp-Plantenga, M. S. Effect of capsaicin on substrate oxidation and weight maintenance after modest body-weight loss in human subjects. *Br. J. Nutr.* **90**, 651–659 (2003).
105. Avesaat, M. Van *et al.* Capsaicin-induced satiety is associated with gastrointestinal distress but not with the release of satiety hormones **103** , 305–313 (2016).
106. Patanè, S., Marte, F., La Rosa, F. C. & La Rocca, R. Capsaicin and arterial hypertensive crisis. *International journal of cardiology* vol. 144 e26-7 (2010).
107. National Institutes of Health Office of Dietary Supplements. Available at: https://ods.od.nih.gov/factsheets/Carnitine-HealthProfessional/ (2017). (Accessed July 13, 2020).
108. Jl, E., Rj, P., Pr, J., Pj, H. & Ji, M. Carnitine does not improve weight loss outcomes in valproate-treated bipolar patients consuming an energy-restricted , low-fat diet. 503–507 (2006).
109. Pooyandjoo, M., Nouhi, M., Shab-Bidar, S., Djafarian, K. & Olyaeemanesh, A. The effect of (L-)carnitine on weight loss in adults: a systematic review and meta-analysis of randomized controlled trials. *Obes. Rev. an Off. J. Int. Assoc. Study Obes.* **17**, 970–976 (2016).
110. Goa, K. L. & Brogden, R. N. l-Carnitine. *Drugs* **34**, 1–24 (1987).
111. Chin, S. F., Storkson, J. M., Albright, K. J., Cook, M. E. & Pariza, M. W. Conjugated linoleic acid is a growth factor for rats as shown by enhanced weight gain and improved feed efficiency. *J. Nutr.* **124**, 2344–2349 (1994).
112. Schmid, A., Collomb, M., Sieber, R. & Bee, G. Conjugated linoleic acid in meat and meat products: A review. *Meat Sci.* **73**, 29–41 (2006).
113. Whigham, L. D., Watras, A. C. & Schoeller, D. A. Efficacy of conjugated linoleic acid for reducing fat mass: a meta-analysis in humans. *Am. J. Clin. Nutr.* **85**, 1203–1211 (2007).
114. Whigham, L. D., O'Shea, M., Mohede, I. C. M., Walaski, H. P. & Atkinson, R. L. Safety profile of conjugated linoleic acid in a 12-month trial in obese humans. *Food Chem. Toxicol. an Int. J. Publ. Br. Ind. Biol. Res. Assoc.* **42**, 1701–1709 (2004).
115. Clément, L. *et al.* hyperinsulinemia and fatty liver in the mouse. **43**, (2002).
116. Farah, A., Monteiro, M., Donangelo, C. M. & Lafay, S. Chlorogenic acids from green coffee extract are highly bioavailable in humans. *J. Nutr.* **138**, 2309–2315 (2008).
117. Shimoda, H., Seki, E. & Aitani, M. Inhibitory effect of green coffee bean extract on fat accumulation and body weight gain in mice. *BMC Complement. Altern. Med.* **6**, 1–9 (2006).
118. Sanlier, N., Atik, A. & Atik, I. Consumption of green coffee and the risk of chronic diseases. *Crit. Rev. Food Sci. Nutr.* **59**, 2573–2585 (2019).
119. Santana-Gálvez, J., Cisneros-Zevallos, L. & Jacobo-Velázquez, D. A. Chlorogenic Acid: Recent advances on its dual role as a food additive and a nutraceutical against metabolic syndrome. *Molecules* **22**, 7–9 (2017).
120. Alonso-Castro, A. J., Miranda-Torres, A. C., González-Chávez, M. M. & Salazar-Olivo, L. A. Cecropia obtusifolia Bertol and its active compound, chlorogenic acid, stimulate 2-NBDglucose uptake in both insulin-sensitive and insulin-resistant 3T3 adipocytes. *J. Ethnopharmacol.* **120**, 458–464 (2008).
121. Johnston, K. L., Clifford, M. N. & Morgan, L. M. Coffee acutely modifies gastrointestinal hormone secretion and glucose tolerance in humans: glycemic effects of chlorogenic acid and caffeine. *Am. J. Clin. Nutr.* **78**, 728–733 (2003).
122. Matsui, T., Ogunwande, I., Abesundara, K. & Matsumoto, K. Anti-hyperglycemic Potential of Natural Products. *Mini Rev. Med. Chem.* **6**, 349–356 (2006).
123. Ong, K. W., Hsu, A. & Tan, B. K. H. Anti-diabetic and anti-lipidemic effects of chlorogenic acid are mediated by ampk activation. *Biochem. Pharmacol.* **85**, 1341–1351 (2013).
124. Onakpoya, I., Terry, R. & Ernst, E. The Use of Green Coffee Extract as a Weight Loss Supplement: A Systematic Review and Meta-Analysis of Randomised Clinical Trials. *Gastroenterol. Res. Pract.* **2011**, (2011).
125. Musial, C., Kuban-Jankowska, A. & Gorska-Ponikowska, M. Beneficial Properties of Green Tea Catechins. *Int. J. Mol. Sci.* **21**, 1744 (2020).
126. Jeukendrup, A. & Randell, R. Fat burners: Nutrition supplements that increase fat metabolism. *Obes. Rev.* **12**, 841–851 (2011).
127. Dulloo, A. G. *et al.* Efficacy of a green tea extract rich in catechin polyphenols and caffeine in

increasing 24-h energy expenditure and fat oxidation in humans. *Am. J. Clin. Nutr.* **70**, 1040–1045 (1999).
128. Westerterp-plantenga, M. S., Lejeune, M. P. G. M. & Kovacs, E. M. R. Body Weight Loss and Weight Maintenance in Relation to Habitual Caffeine Intake and Green Tea Supplementation. (2005).
129. Hursel, R., Viechtbauer, W. & Westerterp-Plantenga, M. S. The effects of green tea on weight loss and weight maintenance: a meta-analysis. *Int. J. Obes. (Lond).* **33**, 956–961 (2009).
130. Oketch-Rabah, H. A. *et al.* United States Pharmacopeia (USP) comprehensive review of the hepatotoxicity of green tea extracts. *Toxicology Reports* vol. 7 386–402 (2020).
131. Watson, J. A., Fang, M. & Lowenstein, J. M. Tricarballylate and hydroxycitrate: substrate and inhibitor of ATP: citrate oxaloacetate lyase. *Arch. Biochem. Biophys.* **135**, 209–217 (1969).
132. Kornacker, M. & Lowenstein, J. Citrate and the Conversion of Carbohydrate Into Fat. the Activities of Citrate-Cleavage Enzyme and Acetate Thiokinase in Livers of Starved and Re-Fed Rats. *Biochem. J.* **94**, 209–215 (1965).
133. Bressler, R. & Brendel, K. The role of carnitine and carnitine acyltransferase in biological acetylations and fatty acid synthesis. *J. Biol. Chem.* **241**, 4092–4097 (1966).
134. Linn, T. C. & Srere, P. A. Identification of ATP citrate lyase as a phosphoprotein. *J. Biol. Chem.* **254**, 1691–1698 (1979).
135. Sullivan, A. C., Hamilton, J. G., Miller, O. N. & Wheatley, V. R. Inhibition of lipogenesis in rat liver by (-)-hydroxycitrate. *Arch. Biochem. Biophys.* **150**, 183–190 (1972).
136. Jena, B. S., Jayaprakasha, G. K., Singh, R. P. & Sakariah, K. K. Chemistry and biochemistry of (-)-hydroxycitric acid from *Garcinia*. *J. Agric. Food Chem.* **50**, 10–22 (2002).
137. Onakpoya, I., Hung, S. K., Perry, R., Wider, B. & Ernst, E. The Use of *Garcinia* Extract (Hydroxycitric Acid) as a Weight loss Supplement: A Systematic Review and Meta-Analysis of Randomised Clinical Trials. *J. Obes.* **2011**, 509038 (2011).
138. Crescioli, G. *et al.* Acute liver injury following Garcinia cambogia weight-loss supplementation: case series and literature review. *Intern. Emerg. Med.* **13**, 857–872 (2018).
139. LiverTox. Clinical and research information on drug-induced liver injury Bethesda (MD): National institute of diabetes and digestive and kidney diseases. *Garcinia cambogia*. Available at: https://www.ncbi.nlm.nih.gov/books/NBK548087/ (2012). (Accessed February 13, 2019).
140. McCarty, M. F., and Majeed, M. The pharmacology of citrin, in *Citrin: a ReVolutionary herbal approach to weight management*. Editor M. Majeed (Burlingame, CA: New Editions Publishing), 34–51 (1994).
141. van Heerden, F. R. Hoodia gordonii: a natural appetite suppressant. *J. Ethnopharmacol.* **119**, 434–437 (2008).
142. Novel food catalogue. Available at: https://webgate.ec.europa.eu/fip/novel_food_catalogue/. (Accessed October 13, 2022).
143. MacLean, D. B. & Luo, L.-G. Increased ATP content/production in the hypothalamus may be a signal for energy-sensing of satiety: studies of the anorectic mechanism of a plant steroidal glycoside. *Brain Res.* **1020**, 1–11 (2004).
144. Blom, W. A. M. *et al.* Effects of 15-d repeated consumption of *Hoodia gordonii* purified extract on safety, ad libitum energy intake, and body weight in healthy, overweight women: a randomized controlled trial. *Am. J. Clin. Nutr.* **94**, 1171–1181 (2011).
145. Roza, O., Lovász, N., Zupkó, I., Hohmann, J. & Csupor, D. Sympathomimetic Activity of a *Hoodia gordonii* Product: A Possible Mechanism of Cardiovascular Side Effects. *Biomed Res. Int.* **2013**, 171059 (2013).
146. Lemus-Mondaca, R., Vega-Gálvez, A., Zura-Bravo, L. & Kong, A. H. *Stevia rebaudiana* Bertoni, source of a high-potency natural sweetener: A comprehensive review on the biochemical, nutritional and functional aspects. *Food Chem.* **132**, 1121–1132 (2012).
147. Samuel, P. *et al.* Stevia Leaf to Stevia Sweetener: Exploring Its Science, Benefits, and Future Potential. *J. Nutr.* **148**, 1186S-1205S (2018).
148. Momtazi-Borojeni, A. A., Esmaeili, S.-A., Abdollahi, E. & Sahebkar, A. A Review on the Pharmacology and Toxicology of Steviol Glycosides Extracted from Stevia rebaudiana. *Curr. Pharm. Des.* **23**, 1616–1622 (2017).
149. European Commission. Regulation (EU) Nº 1131/2011 of 11 November 2011 amending Annex II to Regulation (EC) No 1333/2008 of the European Parliament and of the Council with regard to steviol glycosides. *Off. J. Eur. Union* **2011**, 205–211 (2011).

150. Centre for the Promotion of Imports from developing countries (CBI). Entering the European market for stevia Available at: https://www.cbi.eu/market-information/natural-food-additives/stevia/market-entry (2022) (Accessed January 23, 2023)
151. European Commission. Regulation (EC) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers. Off. J. Eur. Union **304**, 18–63 (2011).
152. European Parliament and Council. Regulation (EC) Nº 178/2002 of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. *Off. J. Eur. Communities* **L31**, 1–24 (2002).
153. *European Food Safety Authority*.Sweeteners. Available at: https://www.efsa.europa.eu/en/topics/topic/sweeteners (2019) (Accessed January 23, 2023)
154. European Parliament and the Concil of the European Union. Regulation (EC) No 1333/2008 of the European Parliament ans of the Council of 16 December 2998 on food additives. *Off. J. Eur. Union* 16–33 (2008).
155. European Commission. Regulation (EC) No 1334/2008. *Off. J. Eur. Union, 2008* **L 354**, 34–50 (2008).
156. European Commission. Regulation (EC) No 2021/1156. *Off. J. Eur. Union, 2021* **L 249**, 87-98 (2021).
157. European Commission. Regulation (EC) No 2016/1814. *Off. J. Eur. Union, 2006* **L 278**, 37-41 (2016).
158. Clement, B. A., Goff, C. M. & Forbes, T. D. A. Toxic amines and alkaloids from *Acacia rigidula*. *Phytochemistry* **49**, 1377–1380 (1998).
159. Koncz, D., Tóth, B., Kiss, T., Roza, O. & Csupor, D. *Acacia rigidula* versus other *Acacia* taxa: An alarming issue in the European novel food regulation and food supplement industry. *Acta Pharm. Hung.* **91**, 67–74 (2021).
160. Stohs, S. J., Preuss, H. G. & Shara, M. The safety of *Citrus aurantium* (bitter orange) and its primary protoalkaloid p-synephrine. *Phyther. Res.* **25**, 1421–1428 (2011).
161. Ruiz-Moreno, C., Coso, J. Del, Giráldez-Costas, V., González-García, J. & Gutiérrez-Hellín, J. Effects of *p*-synephrine during exercise: A brief narrative review. *Nutrients* **13**, 1–9 (2021).
162. Haaz, S. *et al. Citrus aurantium* and synephrine alkaloids in the treatment of overweight and obesity: An update. *Obes. Rev.* **7**, 79–88 (2006).
163. Andrade, A. S., Schmitt, G. C., Rossato, L. G., Russowsky, D. & Limberger, R. P. Gas chromatographic method for analysis of *p*-synephrine in *Citrus aurantium* L. Products. *Chromatographia* **69**, S225–S229 (2009).
164. Arbo, M. D. *et al.* Concentrations of p-synephrine in fruits and leaves of Citrus species (Rutaceae) and the acute toxicity testing of *Citrus aurantium* extract and *p*-synephrine. *Food Chem. Toxicol.* **46**, 2770–2775 (2008).
165. Fugh-Berman, A. & Myers, A. *Citrus aurantium*, an ingredient of dietary supplements marketed for weight loss: Current status of clinical and basic research. *Exp. Biol. Med.* **229**, 698–704 (2004).
166. Pawar, R. S. & Grundel, E. Overview of regulation of dietary supplements in the USA and issues of adulteration with phenethylamines (PEAs). *Drug Test. Anal.* **9**, 500–517 (2017).
167. Stohs, S. J. Safety, Efficacy, and Mechanistic Studies Regarding *Citrus aurantium* (Bitter Orange) Extract and *p*-Synephrine. *Phyther. Res.* **31**, 1463–1474 (2017).
168. Vaysse, J. *et al.* Analysis of adulterated herbal medicines and dietary supplements marketed for weight loss by DOSY 1H-NMR. *Food Addit. Contam. - Part A Chem. Anal. Control. Expo. Risk Assess.* **27**, 903–916 (2010).
169. Cohen, P. A. *et al.* Pharmaceutical doses of the banned stimulant oxilofrine found in dietary supplements sold in the USA. *Drug Test. Anal.* **9**, 135–142 (2017).
170. Thomas, J. E., Munir, J. A., McIntyre, P. Z. & Ferguson, M. A. STEMI in a 24-year-old man after use of a synephrine-containing dietary supplement: A case report and review of the literature. *Texas Hear. Inst. J.* **36**, 586–590 (2009).
171. Palamar, J. How ephedrine escaped regulation in the United States: a historical review of misuse and associated policy. *Health Policy (New. York).* **99**, 1–9 (2011).
172. *European Food Safety Authority*. Scientific Opinion on safety evaluation of *Ephedra* species for use in food. *EFSA J.* **11**, 1–79 (2013).
173. Colker, C. M., Kalman, D. S., Torina, G. C., Perlis, T. & Street, C. Effects of *Citrus aurantium* extract, caffeine, and St. John's Wort on body fat loss, lipid levels, and mood states in overweight healthy adults. *Curr. Ther. Res. Exp.* **60**, 145–153 (1999).
174. Arch, J. R. S. β3-Adrenoceptor agonists: potential, pitfalls and progress. *Eur. J. Pharmacol.* **440**, 99–

107 (2002).
175. Jones, D. Citrus and ephedra. *Whole Foods* **40**, (2004).
176. Haller, C. A. & Benowitz, N. L. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. *N. Engl. J. Med.* **343**, 1833–1838 (2000).
177. Rossato, L. G., Stohs, S. J. & J., S. Synephrine: From trace concentrations to massive consumption in weight-loss. *Food Chem. Toxicol.* **49**, 1472–1473 (2011).
178. Haller, C. A., Duan, M., Jacob III, P. & Benowitz, N. Human pharmacology of a performance-enhancing dietary supplement under resting and exercise conditions. *Br. J. Clin. Pharmacol.* **65**, 833–840 (2008).
179. Bakhyia, N. *et al.* Risk assessment of synephrine in dietary supplements. *Bundesgesundheitsblatt. Gesundheitsforschung. Gesundheitsschutz* **60**, 323–331 (2017).
180. *European* Parliament. Directive 2002/46/CE. *Off. J. Eur. Communities* 51–57 (2002).
181. Haššo, M., Sarakhman, O., Stanković, D. M. & Švorc, Ĺ. A new voltammetric platform for reliable determination of the sport performance-enhancing stimulant synephrine in dietary supplements using a boron-doped diamond electrode. *Anal. Methods* **12**, 4749–4758 (2020).
182. ANSES. Opinion of the French agency for food, environmental and occupational health & safety on the risks associated with the presence in food supplements of psynephrine or ingredients obtained from *Citrus* spp. fruits containing this substance. **33**, 27–31 (2014).
183. Czepielewska, E., Makarewicz-Wujec, M., Różewski, F., Wojtasik, E. & Kozłowska-Wojciechowska, M. Drug adulteration of food supplements: A threat to public health in the European Union? *Regul. Toxicol. Pharmacol.* **97**, 98–102 (2018).
184. Rocha, T., Amaral, J. S. & Oliveira, M. B. P. P. Adulteration of dietary supplements by the illegal addition of synthetic drugs: a review. *Compr. Rev. food Sci. food Saf.* **15**, 43–62 (2016).
185. Kennedy, C., Brewer, L. & Williams, D. Drug interactions. *Med. (United Kingdom)* **44**, 422–426 (2016).
186. Ruiz, M. Risks of Self-Medication Practices. *Curr. Drug Saf.* **5**, 315–323 (2010).
187. Pádua, I., Moreira, A., Moreira, P., Melo de Vasconcelos, F. & Barros, R. Impact of the regulation (EU) 1169/2011: Allergen-related recalls in the rapid alert system for food and feed (RASFF) portal. *Food Control* **98**, 389–398 (2019).
188. Anadón, A., Ares, I., Martínez-Larrañaga, M.-R. & Martínez, M.-A. Chapter 73 - Evaluation and regulation of food supplements: European perspective. in *Nutraceuticals (Second Edition)* (eds. Gupta, R. C., Lall, R. & Srivastava, A.) 1241–1271 (Academic Press, 2021).
189. Samenuk, D. *et al.* Adverse cardiovascular events temporally associated with ma huang, an herbal source of ephedrine. *Mayo Clin. Proc.* **77**, 12–16 (2002).
190. Astell, K. J., Mathai, M. L. & Su, X. Q. Plant extracts with appetite suppressing properties for body weight control: a systematic review of double blind randomized controlled clinical trials. *Complement. Ther. Med.* **21**, 407–416 (2013).
191. Pittler, M. H. & Ernst, E. Guar gum for body weight reduction: meta-analysis of randomized trials. *Am. J. Med.* **110**, 724–730 (2001).
192. Poddar, K., Kolge, S., Bezman, L., Mullin, G. E. & Cheskin, L. J. Nutraceutical supplements for weight loss: a systematic review. *Nutr. Clin. Pract. Off. Publ. Am. Soc. Parenter. Enter. Nutr.* **26**, 539–552 (2011).
193. Dwyer, J. T., Allison, D. B. & Coates, P. M. Dietary supplements in weight reduction. *J. Am. Diet. Assoc.* **105**, S80-6 (2005).
194. European Parliament and the Council of the European Union. Regulation (EU) 2015/2283 of the European Parliament and of the Council of 25 November 2015 on novel foods, amending Regulation (EU) No 1169/2011 of the European Parliament and of the Council and repealing Regulation (EC) No 258/97 etc. *Off. J. Eur. Union* **327**, 1–22 (2015).
195. European Commission. Commission implementing regulation (EU) 2017/2470 of 20 December 2017 establishing the Union list of novel foods in accordance with Regulation (EU) 2015/2283 of the European Parliament and of the Council on novel foods. *Off. J. Eur. Union* **351**, 72–201 (2017).
196. Kliszczewicz, B. *et al.* The influence of citrus aurantium and caffeine complex versus placebo on the cardiac autonomic response: a double blind crossover design. *J. Int. Soc. Sports Nutr.* **15**, 34 (2018).
197. Rashti, S. L. *et al.* Thermogenic effect of meltdown RTD energy drink in young healthy women: A double blind, cross-over design study. *Lipids Health Dis.* **8**, (2009).

198. Penzak, S. R. *et al.* Seville (sour) orange juice: Synephrine content and cardiovascular effects in normotensive adults. *J. Clin. Pharmacol.* **41**, 1059–1063 (2001).
199. Bui, L. T., Nguyen, D. T. T. & Ambrose, P. J. Blood pressure and heart rate effects following a single dose of bitter orange. *Ann. Pharmacother.* **40**, 53–57 (2006).
200. Hoffman, J. R. *et al.* Thermogenic effect of an acute ingestion of a weight loss supplement. *J. Int. Soc. Sports Nutr.* **6**, 1–9 (2009).
201. Jung, Y. P. *et al.* Effects of acute ingestion of a pre-workout dietary supplement with and without p-synephrine on resting energy expenditure, cognitive function and exercise performance. *J. Int. Soc. Sports Nutr.* **14**, 3 (2017).
202. Min, B., Cios, D., Kluger, J. & White, C. M. Absence of QTc-interval-prolonging or hemodynamic effects of a single dose of bitter-orange extract in healthy subjects. *Pharmacotherapy* **25**, 1719–1724 (2005).
203. Seifert, J. G., Nelson, A., Devonish, J., Burke, E. R. & Stohs, S. J. Effect of acute administration of an herbal preparation on blood pressure and heart rate in humans. *Int. J. Med. Sci.* **8**, 192–197 (2011).
204. Shara, M., Stohs, S. J. & Mukattash, T. L. Cardiovascular Safety of Oral *p*-Synephrine (Bitter Orange) in Healthy Subjects: A Randomized Placebo-Controlled Cross-over Clinical Trial. *Phyther. Res.* **30**, 842–847 (2016).
205. Benjamim, C. J. R. *et al.* Bitter Orange (*Citrus aurantium* L.) Intake Before Submaximal Aerobic Exercise Is Safe for Cardiovascular and Autonomic Systems in Healthy Males: A Randomized Trial. *Front. Nutr.* **9**, 890388 (2022).
206. Jung, Y. P. *et al.* Effects of ingesting a pre-workout dietary supplement with and without synephrine for 8 weeks on training adaptations in resistance-trained males. *J. Int. Soc. Sports Nutr.* **14**, 1 (2017).
207. Kaats, G. R., Miller, H., Preuss, H. G. & Stohs, S. J. A 60 day double-blind, placebo-controlled safety study involving *Citrus aurantium* (bitter orange) extract. *Food Chem. Toxicol.* **55**, 358–362 (2013).
208. Kalman, D. S., Colker, C. M., Shi, Q. & Swain, M. A. Effects of a weight-loss aid in healthy overweight adults: Double-blind, placebo-controlled clinical trial. *Curr. Ther. Res. - Clin. Exp.* **61**, 199–205 (2000).
209. Stohs, S. J. *et al.* Effects of *p*-synephrine alone and in combination with selected bioflavo-noids on resting metabolism, blood pressure, heart rate and self-reported mood changes. *Int. J. Med. Sci.* **8**, 295–301 (2011).
210. Bush, J. A. *et al.* Acute hematological and mood perception effects of bitter orange extract (*p*-synephrine) consumed alone and in combination with caffeine: A placebo-controlled, double-blind study. *Phyther. Res.* **32**, 1593–1607 (2018).
211. Ratamess, N. A. *et al.* Acute cardiovascular effects of bitter orange extract (*p*-synephrine) consumed alone and in combination with caffeine in human subjects: A placebo-controlled, double-blind study. *Phyther. Res.* **32**, 94–102 (2018).
212. Gutierrez-Hellin, J. & Del Coso, J. Dose-Response Effects of *p*-Synephrine on Fat Oxidation Rate During Exercise of Increasing Intensity. *Phyther. Res.* **32**, 370–374 (2018).
213. Gutierrez-Hellin, J., Ruiz-Moreno, C. & Del Coso, J. Acute *p*-synephrine ingestion increases whole-body fat oxidation during 1-h of cycling at Fatmax. *Eur. J. Nutr.* **59**, 3341–3345 (2020).
214. Sale, C., Harris, R. C., Delves, S. & Corbett, J. Metabolic and physiological effects of ingesting extracts of bitter orange, green tea and guarana at rest and during treadmill walking in overweight males. *Int. J. Obes.* **30**, 764–773 (2006).
215. Gutiérrez-Hellín, J. & Del Coso, J. Acute *p*-synephrine ingestion increases fat oxidation rate during exercise. *Br. J. Clin. Pharmacol.* 362–368 (2016).
216. Cann, H. M. & Verhulst, H. L. Fatality from acute dinitrophenol derivative poisoning. *Am. J. Dis. Child.* **100**, 947–948 (1960).
217. Macbryde, C. M. & Taussig, B. L. Functional Changes in liver, heart and muscles, and loss of dextrose tolerance: resulting from dinitrophenol. *J. Am. Med. Assoc.* **105**, 13–17 (1935).
218. Grundlingh, J., Dargan, P. I., El-Zanfaly, M. & Wood, D. M. 2,4-Dinitrophenol (DNP): A Weight Loss Agent with Significant Acute Toxicity and Risk of Death. *J. Med. Toxicol.* **7**, 205–212 (2011).
219. Stohs, S. J., Shara, M. & Ray, S. D. p-Synephrine, ephedrine, *p*-octopamine and *m*-synephrine: Comparative mechanistic, physiological and pharmacological properties. *Phytother. Res.* **34**, 1838–1846 (2020).
220. Suntar, I., Khan, H., Patel, S., Celano, R. & Rastrelli, L. An overview on *Citrus aurantium* L.: Its functions as food ingredient and therapeutic agent. *Oxid. Med. Cell. Longev.* **2018**, (2018).

221. Park, D., Lee, D. & Lee, Y. P-synephrine stimulates glucose consumption via AMPK in l6 skeletal muscle cells. *Diabetes* **61**, A469–A470 (2012).
222. Kratz, A. *et al.* Effect of marathon running on hematologic and biochemical laboratory parameters, including cardiac markers. *Am. J. Clin. Pathol.* **118**, 856–863 (2002).
223. Simonson, D. C. & DeFronzo, R. A. Indirect calorimetry: methodological and interpretative problems. *Am. J. Physiol. Metab.* **258**, E399–E412 (1990).
224. Pendergast, D. R., Leddy, J. J. & Venkatraman, J. T. A perspective on fat intake in athletes. *J. Am. Coll. Nutr.* **19**, 345–350 (2000).
225. Jeukendrup, A. E., Mensink, M., Saris, W. H. M. & Wagenmakers, A. J. M. Exogenous glucose oxidation during exercise in endurance-trained and untrained subjects. *J. Appl. Physiol.* **82**, 835–840 (1997).
226. Bergman, B. C. & Brooks, G. A. Respiratory gas-exchange ratios during graded exercise in fed and fasted trained and untrained men. *J. Appl. Physiol.* **86**, 479–487 (1999).
227. Ramos-Jiménez, A. *et al.* The Respiratory Exchange Ratio is Associated with Fitness Indicators Both in Trained and Untrained Men: A Possible Application for People with Reduced Exercise Tolerance. *Clin. Med. Circ. Respirat. Pulm. Med.* **2**, CCRPM.S449 (2008).
228. Stohs, S. J., Preuss, H. G. & Shara, M. A review of the human clinical studies involving citrus aurantium (bitter orange) extract and its primary protoalkaloid *p*-synephrine. *Int. J. Med. Sci.* **9**, 527–538 (2012).

ACKNOWLEDGEMENT

The person who I owe the greatest and sincere gratitude is my supervisor Prof. Dezső Csupor, who accepted and supported my scientific aims, ideas, and field while patiently and carefully guided me on the path through academic science. Without him and his trust, the entire project could not have been completed and probably would not exist.

I am very fortunate that I was able to learn from Dr. Barbara Tóth, who was my co-supervisor, during my PhD studies. I cannot express enough how much I appreciate all her support and expertise as my co-supervisor.

They were a constant source of inspiration and education for me. Both of them gave me narrow scientific knowledge that I will always remember and practice, enabling me to continue my scientific goals and keep this aspect in the future. Their encouragement, help and humanity made my scientific research succeed.

I am very grateful for Prof. Judit Hohmann who provided me the opportunity to be a part of the university and made my experiments and research possible.

I also thank my co-authors, Dr. Orsolya Roza, Dr. Tivadar Kiss and Dr. Muh. Akbar Bahar and to my colleagues in the Institute of Pharmacognosy: Dr. Ákos Bajtel, Balázs Kovács, Dr. Dóra Rédei, Attila Horváth, and Klára Horváth-Boros, their collaboration in our articles.

My parents have always encouraged and supported me in my scientific career, and I followed them when choosing biology and chemistry as my areas of interest. They played an enormous role in my PhD, which I want to underline and express my love and gratefulness in this paragraph.

My fiancé, who gives my life and work an essential purpose and is my partner in both science and life made my attitude and conception complete.

ANNEX 1. Available pharmacological treatment possibilities for obese patients in the European Union.

Compound	Approved in the EU	Mechanism of action	Possible adverse effects
Semaglutide	Since 2020	appetite suppressant, and delays gastric emptying	gastrointestinal adverse events
Orlistat	since 1998	Inhibit intestinal lipases	liver damage, vitamin deficiency
Liraglutide	since 2009	appetite suppressant, and delays gastric emptying	hypoglycaemia, diarrhoea, cardiovascular outcomes
Naltrexone-bupropion	since 2015	appetite suppressant /antidepressant	headache, constipation, possible cardiovascular side effects
Phentermine	1956–2012	appetite suppressant	cardiovascular and central nervous system effects

* based on the authorization of the national competent authority, phentermine resinate is available in modified-release capsules in the Czech Republic

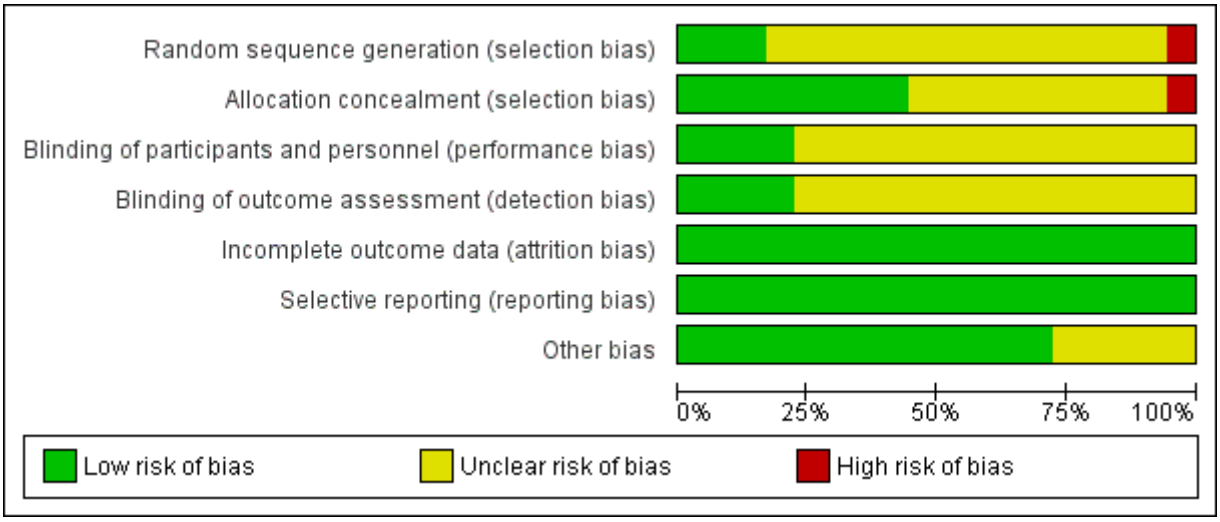
ANNEX 2. Withdrawn amphetamine type medications for obese patients in the European Union.

Ingredient	Approved in the EU	Mechanism of action	Possible adverse effects
Amphetamine	1932–1968	increases noradrenaline, serotonine, and dopamine release	dependence, cardiac complications
PPA	1939–1997	increases noradrenaline, serotonine, and dopamine release	haemorrhagic stroke
Fenfluramine, dexfenfluramine	1963–1997, 1985–1997	increase serotonine release	pulmonary hypertension
Fenfluramine, phentermine (fen-phen)	1984-1997	increase serotonine release, appetite suppressant	pulmonary hypertension

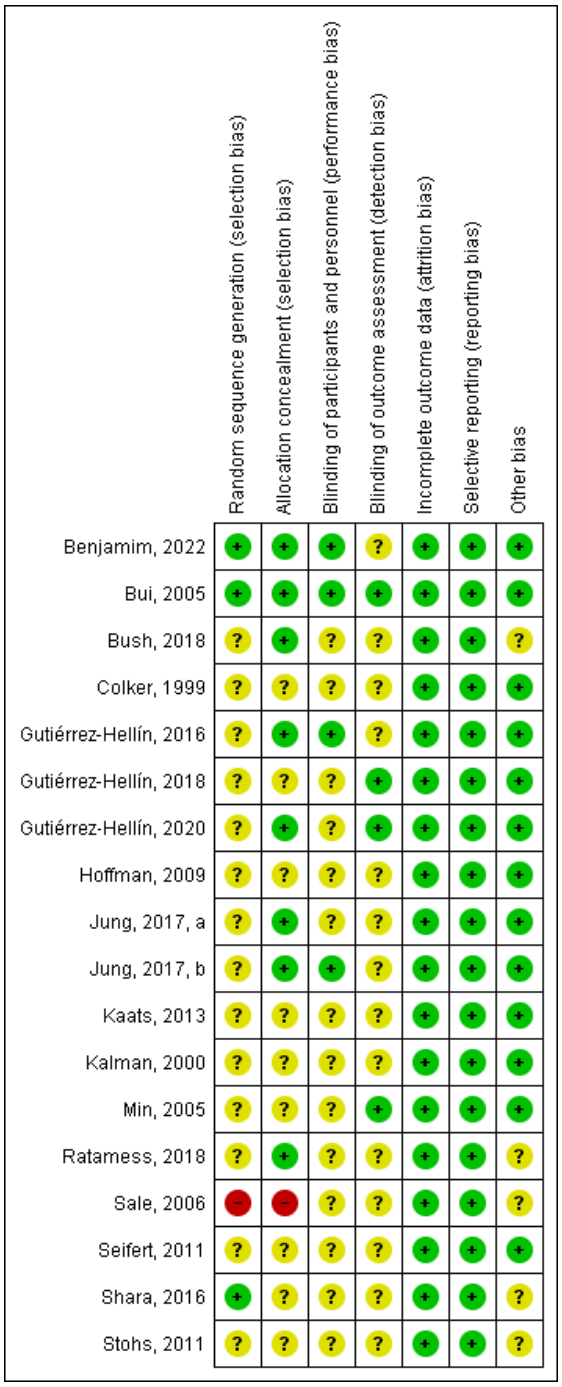
ANNEX 3. Withdrawn non-amphetamine derivative type medications for obese patients in the European Union.

Ingredient	Approved in the EU	Mechanism of action	Possible adverse effects
DNP	1933–1938	increase thermogenesis	hyperthermia
Rimonabant	2006–2009	CB_1-receptor blocker	depressed mood, anxiety, and suicidal ideation
Sibutramine	1999–2010	antidepressant, appetite suppressant	increased systolic and diastolic blood pressure and heart rate
Lorcaserin	2012–2013	increases serotonin release	increased occurrence of cancer

ANNEX 4. Risk of bias graph of the synephrine meta-analysis.



ANNEX 5. Risk of bias summary of the synephrine meta-analysis.

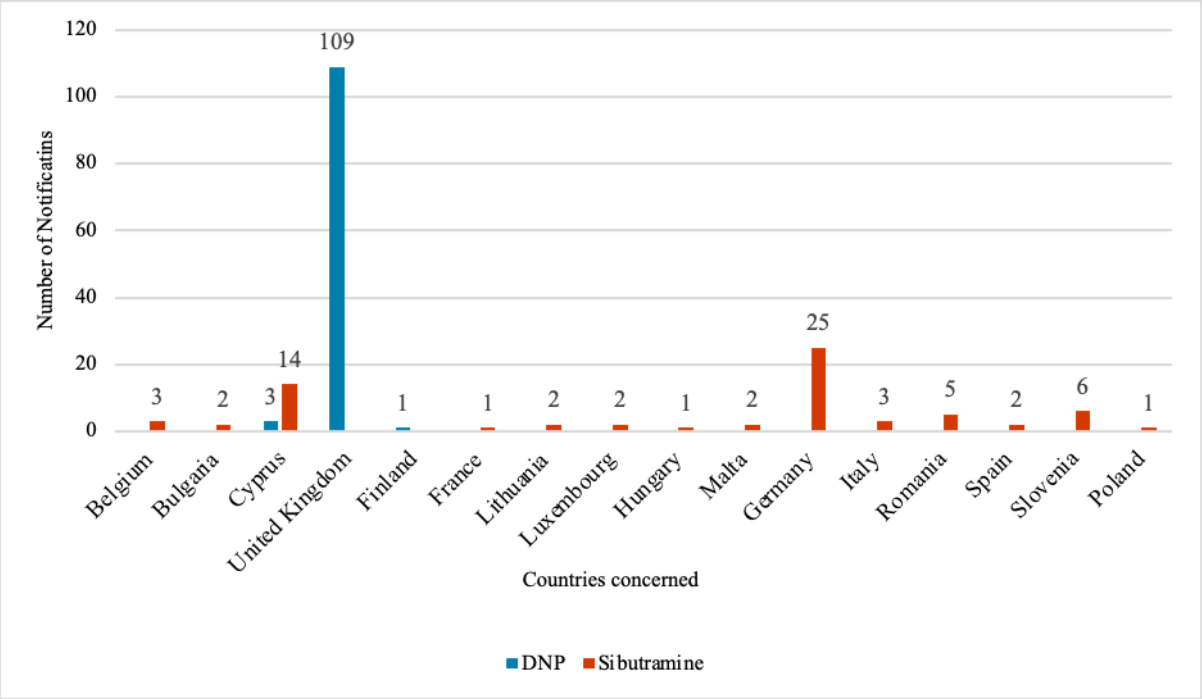


ANNEX 6. Notifications on DNP and sibutramine.

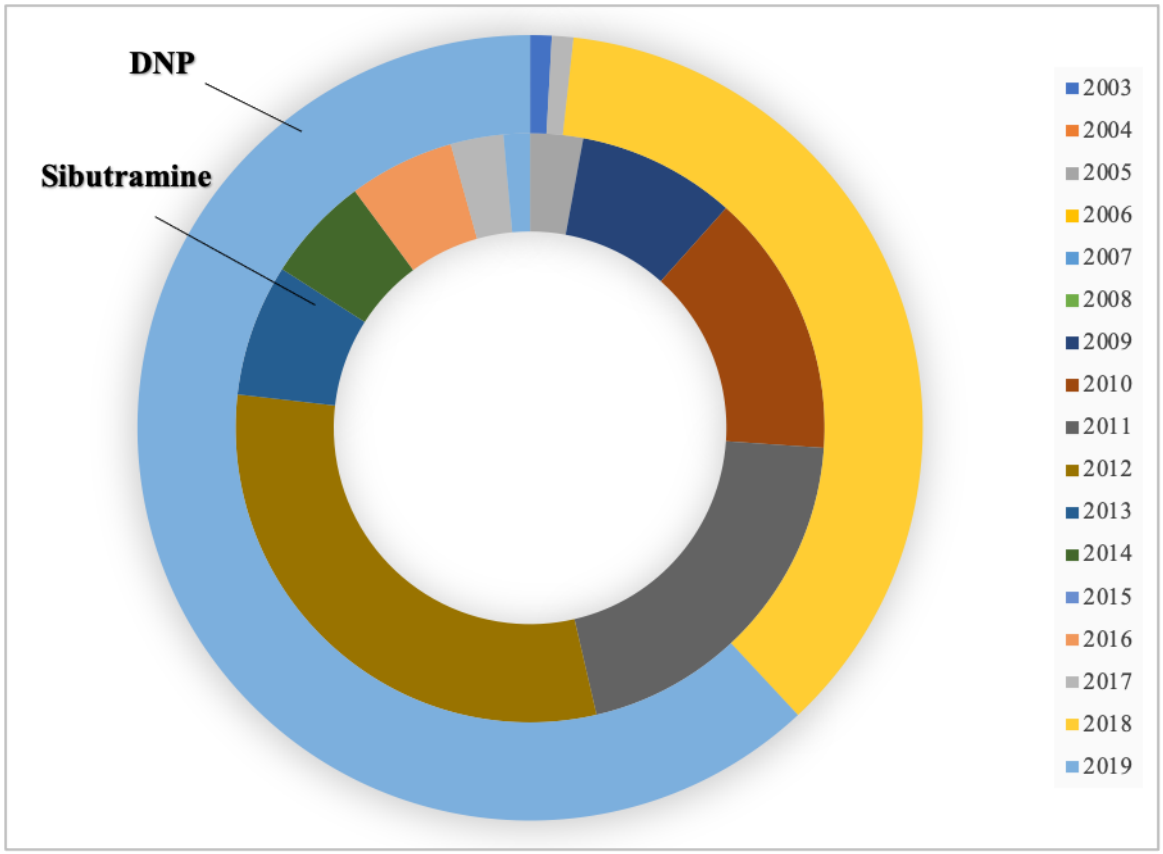
YEAR	DNP		sibutramine	
2003	1	Finland	0	NR*
2004	0	NR*	0	NR*
2005	0	NR*	2	Germany, Poland
2006	0	NR*	0	NR*
2007	0	NR*	0	NR*
2008	0	NR*	0	NR*
2009	0	NR*	6	Romania, Germany, Italy, Cyprus
2010	0	NR*	10	Cyprus, Germany, Italy, Romania, Slovenia
2011	0	NR*	14	Cyprus, Romania, Hungary, Germany, Malta
2012	0	NR*	21	Belgium, Bulgaria, Germany, Lithuania, Luxembourg, Slovenia
2013	0	NR*	5	Belgium, Cyprus, Germany
2014	0	NR*	4	France, Germany
2015	0	NR*	0	NR*
2016	0	NR*	4	Germany, Spain, Cyprus
2017	1	United Kingdom	2	Cyprus, Slovenia
2018	41	United Kingdom	0	NR*
2019	70	United Kingdom, Cyprus	1	Germany

* no reports

ANNEX 7. Notifications on food supplements containing DNP or sibutramine from 2003 to 2019.



ANNEX 8. Ratio of DNP (outside) and sibutramine (inside) from 2003 to 2019.

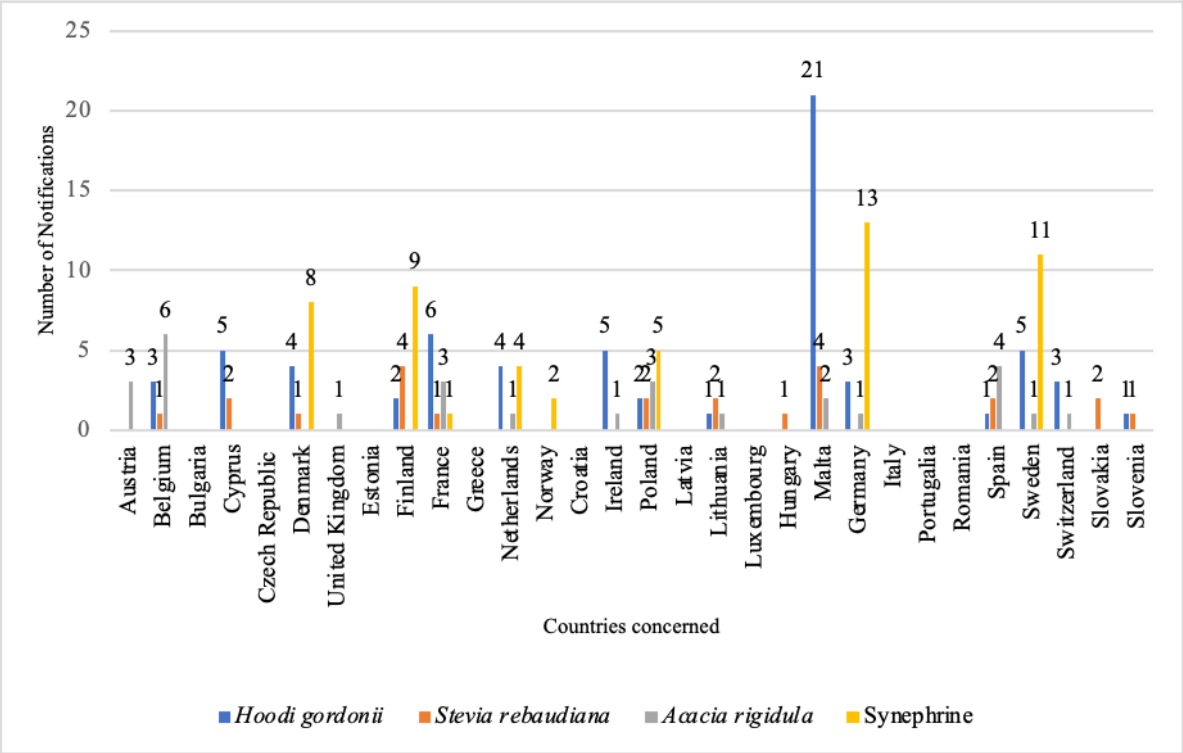


ANNEX 9. Unauthorized *Hoodia gordonii*, *Stevia rebaudiana*, *Acacia rigidula* and synephrine-products (above maximal limit) in the European Union based on RASFF results from 2005 to 2019.

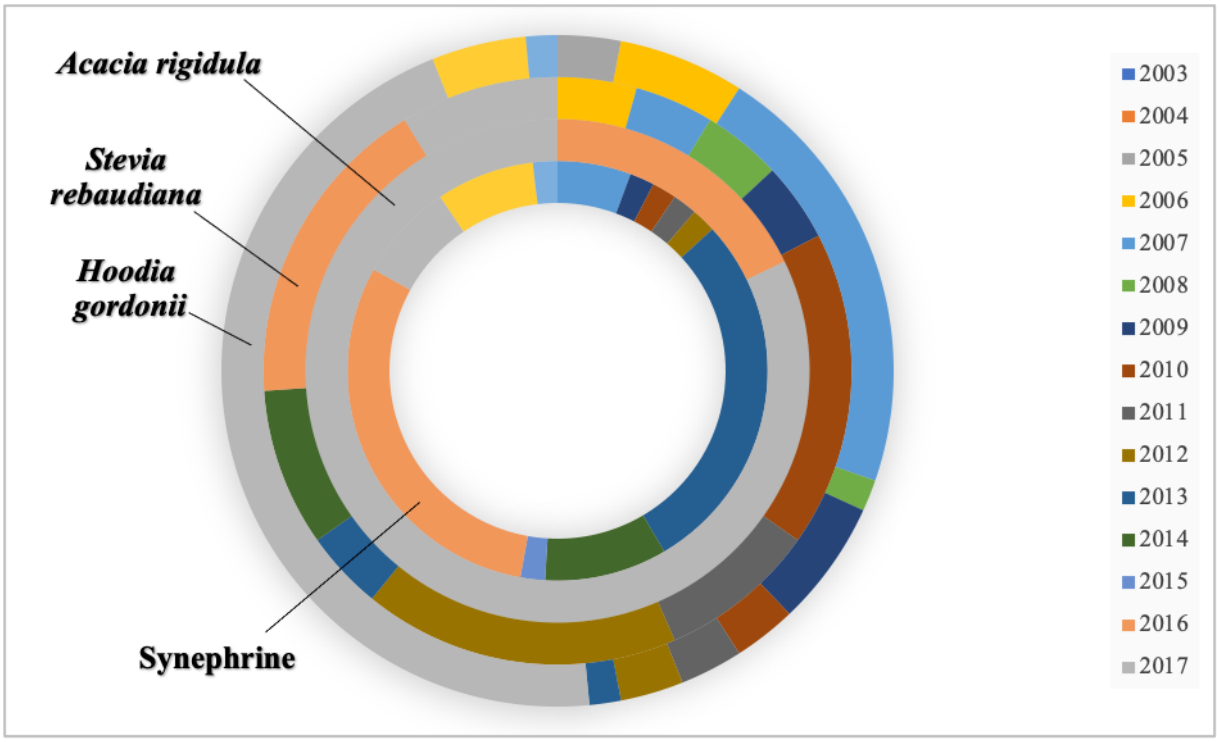
YEAR	*Hoodia goordoni*		*Stevia rebaudiana*		*Acacia rigidula*		**Synephrine**	
2005	2	Netherlands	0	NR*	0	NR*	0	NR*
2006	4	Denmark, Finland, Malta	1	Denmark	0	NR*	0	NR*
2007	14	Malta	1	Malta	0	NR*	3	Norway, Denmark
2008	1	Germany	1	Slovenia	0	NR*	0	NR*
2009	4	Slovenia, Malta	1	Slovakia	0	NR*	1	Poland
2010	2	Ireland, Lithuania	4	Hungary, Belgium, Cyprus	0	NR*	1	Poland
2011	2	Belgium, Germany	2	Malta, Finland	0	NR*	1	France
2012	2	France, Finland	4	Lithuania, France, Finland	0	NR*	1	Sweden
2013	1	Malta	1	Lithuania	0	NR*	15	Finland, Denmark
2014	0	NR*	2	Malta, Finland	0	NR*	5	Poland, Sweden, Germany
2015	0	NR*	0	NR*	0	NR*	1	Norway
2016	0	NR*	4	Poland, Spain, Malta	5	Netherlands, Poland, United Kingdom, Germany	16	Poland, Germany, Sweden, Netherlands
2017	30	Poland, France, Malta, Netherlands, Belgium, Denmark, Switzerland, Cyprus, Ireland, Sweden	2	Slovakia, Spain	23	Poland, Lithuania, France, Malta, Spain, Belgium, Austria, Switzerland, Ireland, Sweden	4	Germany, Sweden
2018	3	Spain, Sweden	0	NR*	NR*	NR*	4	Germany, Sweden
2019	1	Sweden	0	NR*	NR*	NR*	1	Sweden

* no reports

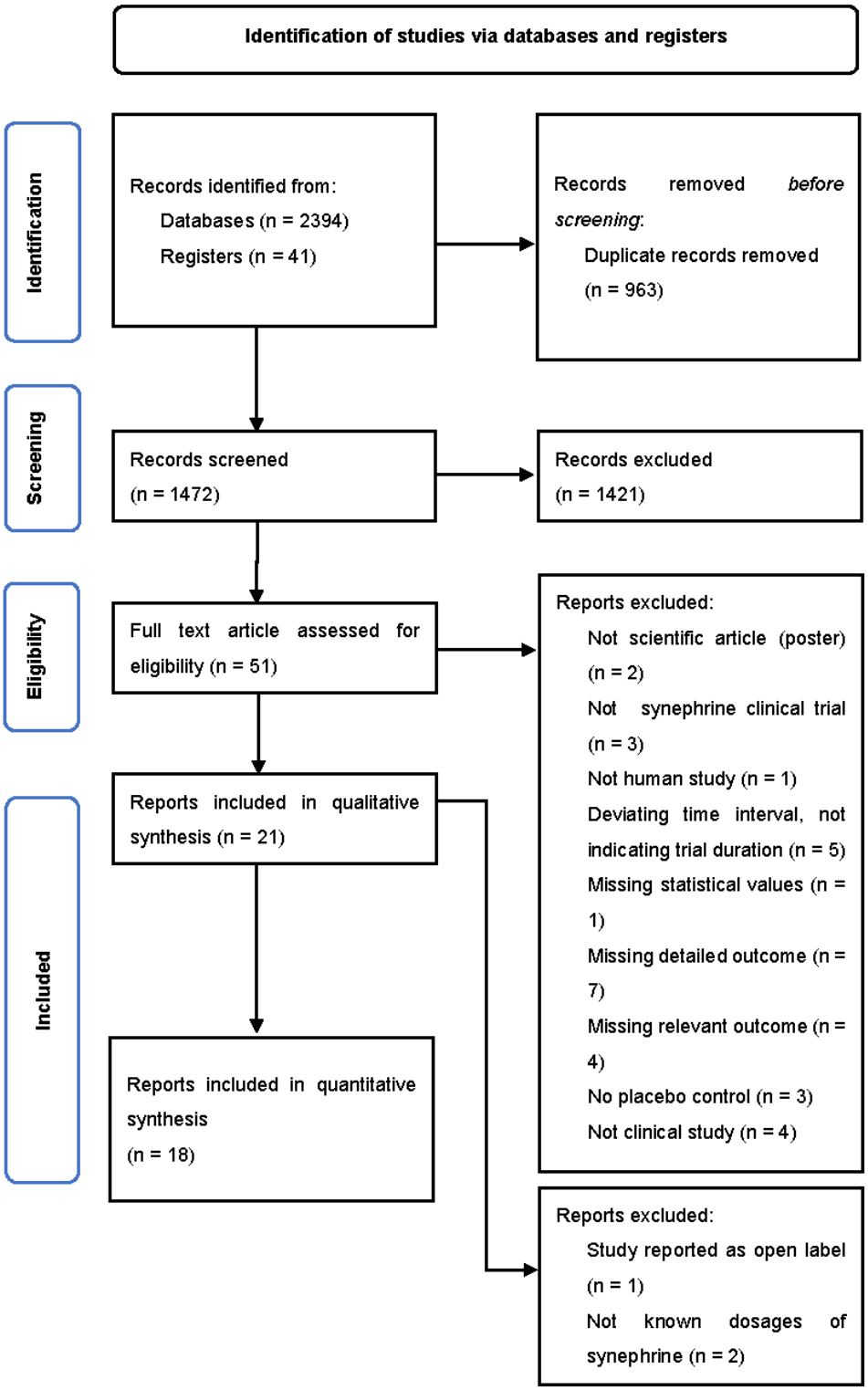
ANNEX 10. Unauthorized *Hoodia gordonii*, *Stevia rebaudiana*, *Acacia rigidula and* synephrine-products from 2003 to 2019.



ANNEX 11. Ratio of *Hoodia gordonii*, (first outer circle) and *Stevia rebaudiana* (second middle circle) and *Acacia rigidula* (third inner circle) synephrine *(*last inner circle) from 2003 to 2019.



ANNEX 12. PRISMA flow diagram for identification of relevant studies.



ANNEX 13. Characteristics of the trials.

Author and year	Synephrine form	Study drug	Dosage	Design
Bui 2006	*p*-	54 mg *p*-synephrine)	2 capsules daily	prospective, crossover study, repeated-measure study design
Bush 2018	*p*-	103 mg	once daily two capsules	within subjects
Colker 1999	*p*-	54 mg *p*-synephrine	once daily	parallel
Guiterrez-Hellín 2016	*p*-	3 mg/kg of *p*-synephrine (average of 214 mg)	once daily	counterbalanced
Guiterrez-Hellín 2018	*p*-	3 mg/kg of *p*-synephrine (average of 203 mg)	once daily	randomized
Guiterrez-Hellín 2020	*p*-	3 mg/kg of *p*-synephrine (average of 213 mg)	once daily	randomized
Hoffman 2009	4-HMP	20 mg of methyl-synephrine HCl	3 capsules daily	crossover
Jung 2017a	*p*-	20 mg	1 serving daily	counterbalanced and crossover manner
Jung 2017b	*p*-	20 mg	1 foil packet per day approximately 15–30 min prior to exercise	parallel, prospective cohort
Kaats 2013	*p*-	24.4 (49 mg daily)	twice daily	parallel
Kalman 2000	*p*-	5 mg	twice daily	parallel
Min 2005	*p*- or *m*-	27 mg	1 tablet dose of bitter-orange dried-fruit extract	crossover
Sale 2006	*p*-	Standardized for synephrine 3 mg (6mg)	2 capsules daily	counterbalanced
Seifert 2011	*p*-	13 mg (total of 52 mg)	4 capsules for a total of 52 mg *p*-synephrine and 704 mg caffeine over a 24-hour period	crossover
Shara 2016	*p*-	49-mg	1 single capsule daily	crossover
Stohs 2011	*p*-	50 mg	1 ounce of juice daily	parallel
Ratamess 2018	*p*-	103 mg	once daily two capsules	within subjects
Benjamim 2022	*p*-	180 mg	once 180 mg synephrine containing capsule	crossover

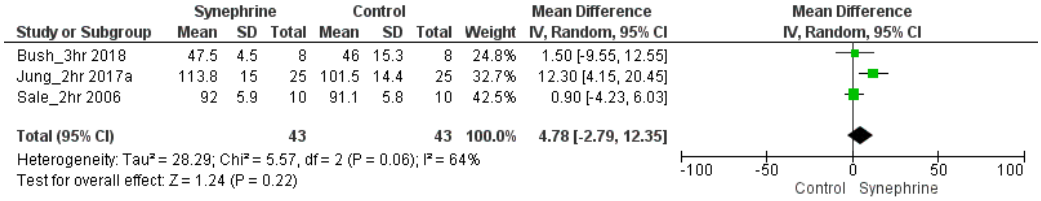
***** *p*- stands for *para*- synephrine; *m*- stands for is *meta*-synephrine (phenylephrine) and 4-HMP means methyl-synephrine HCl

ANNEX 14. Demography of patients.

Author and year	Patients	Average age	Patient randomized	Overall Dropout	Control	Intervention	Male female
Bui 2006	healthy	26 ± 2	15	2	13	13	10 male, 5 female
Bush 2018	healthy and physically active	20.3 ± 1.3	16	2	8	8	10 male, 3 female
Colker 1999	healthy BMI > 25 kg/m2	>21	23	3	7	9	NK
Guiterrez-Hellín 2016	healthy and physically active	26.0 ± 7.2 years	18	0	9	9	NK
Guiterrez-Hellín 2018	healthy and physically active	25.0 ± 7.0 years	13	0	13	13	11 male, 2 female
Guiterrez-Hellín 2020	healthy	31 ± 6.9 years	14	1	13	13	11 male, 2 female
Hoffman 2009	healthy, 71.5 ± 17.2 kg; 17.3 ± 2.6% body fat	20.2 ± 1.2	10	0	10	10	5 male, 5 female
Jung 2017a	healthy (recreationally active)	22 ± 3	26	1	25	25	20 male 5 female
Jung 2017b	healthy, (resistance-trained male)	20.9 ± 3.9	80	0	27	26	80 male
Kaats 2013	healthy	51.3	75	8	25	25	15 male, 60 female
Kalman 2000	healthy but overweight adults, body mass index >27 kg/m^2	42.07-43, 06	30	5	13	12	23 male, 7 female
Min 2005	healthy	24.9 ± 4.4	18	1	18	18	NK
Sale 2006	overweight, sedentary males	27±7	10	1	10	10	10 male
Seifert 2011	mildly overweight individuals	24.7 +7.4	23	0	11	12	9 male, 14 female
Shara 2016	healthy	25	18	0	18	18	9 male, 9 female,
Stohs 2011	healthy	NK	50	0	10	10	NK
Ratamess 2018	healthy	20.3 ± 1.3	16	0	8	8	13 male, 3 female
Benjamim 2022	healthy physically active males	18-30	17	5	12	12	17 male

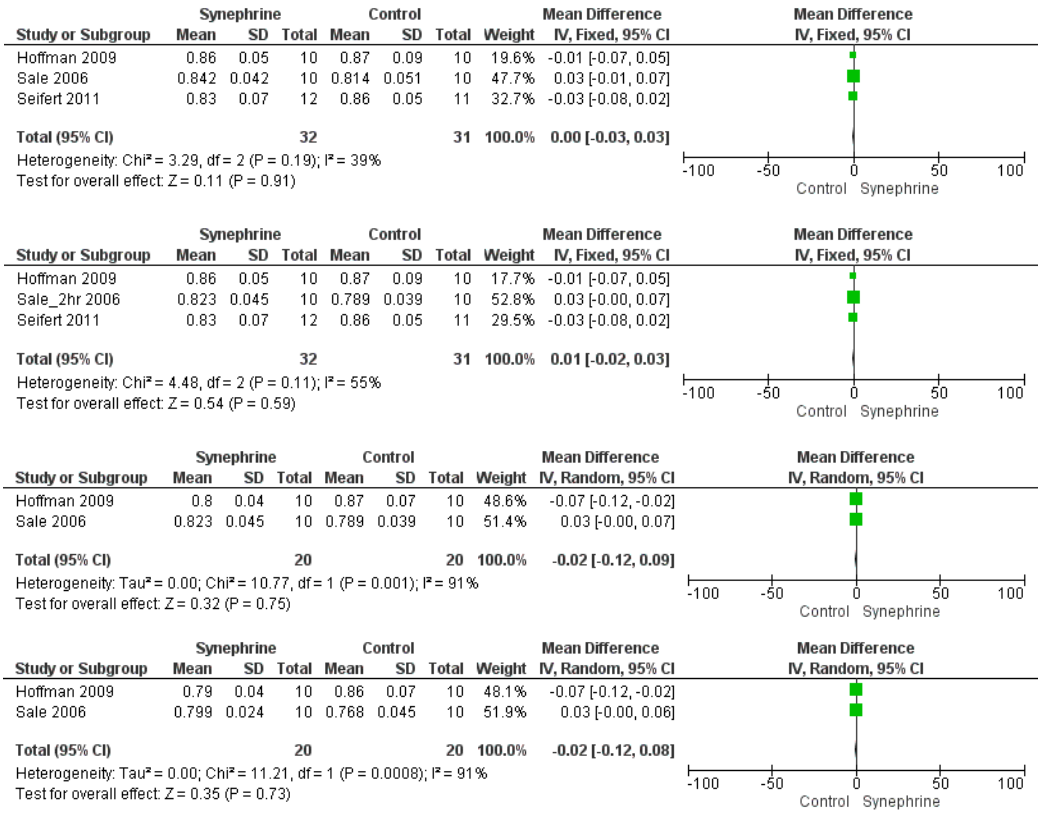
***** NK not known

ANNEX 15. Forest plot diagram of synephrine on blood glucose levels after administering for short time (2–3 hours) in the intervention and in the control groups with one change of the time duration.



(H/**2**)

ANNEX 16. Forest plot diagram of synephrine on RER values 1–3 hours after administration (1 hour two times with one change in time interval) in the intervention and in the control groups.



(I)

APPENDIX

The thesis is based on the following publications:

I. **Koncz, D**., Tóth, B., Roza, O., & Csupor, D. (2021). A Systematic Review of the European Rapid Alert System for Food and Feed: Tendencies in Illegal Food Supplements for Weight Loss. *Frontiers in pharmacology, 11*, 2465. https://doi.org/10.3389/fphar.2020.611361

II. **Koncz, D**., Tóth, B., Bahar, M. A., Roza, O., & Csupor, D. (2022). The Safety and Efficacy of *Citrus aurantium* (Bitter Orange) Extracts and *p*-Synephrine: A Systematic Review and Meta-Analysis. *Nutrients*, 14(19), 4019. https://doi.org/10.3390/nu14194019

frontiers in Pharmacology

SYSTEMATIC REVIEW
published: 26 January 2021
doi: 10.3389/fphar.2020.611361

A Systematic Review of the European Rapid Alert System for Food and Feed: Tendencies in Illegal Food Supplements for Weight Loss

Dorottya Koncz[1], *Barbara Tóth*[1,2], *Orsolya Roza*[1,2] *and Dezső Csupor*[1,2]*

[1]Department of Pharmacognosy, University of Szeged, Szeged, Hungary, [2]Medical School, Institute for Translational Medicine, University of Pécs, Pécs, Hungary

Background: Slimming products represent a dynamically growing group of food supplements worldwide. The efficacy of safely usable natural ingredients is usually below consumers' expectations. Certain manufacturers add unauthorized or prohibited ingredients to weight loss supplements in order to increase their efficacy. Hence, many of these products are adulterated and may pose a risk to the consumers' health.

Aims: The aim of our work was to give an overview on natural ingredients used in slimming products, to summarize the frequently used synthetic adulterants and also to assess the trends of adulterated and illegal food supplements in the European Union based on the warnings of the Rapid Alert System for Food and Feed (RASFF) in the time period of 1988–2019.

Methods: Reports between 1988–2019 were extracted from the RASFF portal on January 1, 2020. Each entry was individually reviewed.

Results: 2,559 records of food supplements with quality problems were identified in the RASFF, several of which [319 (12,5%)] were marketed to facilitate weight loss. 202 (63,3%) contained unapproved, synthetic drug ingredients. The major adulterant (113 of 319, 35.4%) was DNP (2,4-dinitrophenol), whereas sibutramine was the second most frequent adulterant agent (69 products, 21,6%) between 1988 and 2019.

Conclusion: The number of approved medicines for the indication of weight loss is relatively low and their efficacy (and also that of the natural ingredients) is limited. Therefore, a significant number of weight loss supplements is adulterated to satisfy patients' expectations. Hence, these products may cause serious adverse effects in sensitive patients.

OPEN ACCESS

Edited by:
Michał Tomczyk,
Medical University of Bialystok, Poland

Reviewed by:
Eric Deconinck,
Sciensano, Belgium
Jakub Dorożyński,
Department of Family Medicine,
Medical University of Lodz, Poland

***Correspondence:**
Dezső Csupor
csupor.dezso@pharmacognosy.hu

Specialty section:
This article was submitted to Ethnopharmacology, a section of the journal Frontiers in Pharmacology

Received: *28 September 2020*
Accepted: *24 December 2020*
Published: *26 January 2021*

Citation:
Koncz D, Tóth B, Roza O and Csupor D (2021) A Systematic Review of the European Rapid Alert System for Food and Feed: Tendencies in Illegal Food Supplements for Weight Loss. Front. Pharmacol. 11:611361. doi: 10.3389/fphar.2020.611361

Abbreviations: 5-HT2C, 5-hydroxytryptamine; ATP, adenosine triphosphate; BMI, body-mass index; CB1-receptor, cannabinoid receptor type 1; CHMP, Committee for Medicinal Products for Human Use; CLA, conjugated linoleic acid; DNP, 2,4-dinitrophenol; EC, European Commission; EGCG, epigallocatechin-3-gallate; EMA, European Medicines Agency; EU, European Union; FA, fatty acid; GCE, green coffee extract; GLP-1, glucagon like peptide-1; GM, glucomannan; HCA, (-)-hydroxycitric acid; NA, noradrenaline; NR, no reports; POMC, pro-opiomelanocortin; PPA, phenylpropanolamine; RASFF, rapid alert system for food and feed; RCT, randomized controlled trial; SCOUT, sibutramine cardiovascular outcomes trial; T2DM, type 2 diabetes mellitus; WMD, weighted mean difference.

Keywords: food supplements, rapid alert system for food and feed, illegal medicines, obesity, weight loss

INTRODUCTION

Obesity is an emerging health problem worldwide, the number of affected people doubled from 1980 to 2008 (Finucane et al., 2011). Not only the incidence of obesity has been growing, but the world's population's mean BMI has also been increasing by a significant 0.4–0.5 kg/m^2 in each decade (Finucane et al., 2011). Based on the World Health Organization's (WHO) estimates, almost two billion adults had a body-mass index (BMI) ≥ 25.0 and of these adults more than 650 million people were classified as obese (BMI ≥30.0) in 2016 (World Health Organisation, 2018; Montan et al., 2019). Obesity does not only affect the United States, but it is becoming an epidemic also in Europe and even in several developing countries (Barness et al., 2007). According to a recently issued report, approximately 23% of the female and 20% of the male population of Europe were considered obese (World Health Organisation, 2019). If game-changing measures are not going to be applied, by the end of this decade, more than half of the world's adult population will be obese or at least overweight (Kelly et al., 2008). Obesity is associated with many comorbidities, including cardiovascular (e.g. heart disease, hypertension) and cerebrovascular (e.g. stroke) ailments. The incidence of other severe chronic diseases, such as type 2 diabetes mellitus (T2DM) and degenerative musculoskeletal diseases (e.g. arthritis) are higher among overweight and obese people than among people with normal BMI. Moreover, Alzheimer's disease and some malignant tumors affect more often obese people (World Health Organisation, 2018). Lifestyle interventions, involving dietary modifications and increased physical activity are of high importance in avoiding obesity; however, a high proportion of the individuals loses interest shortly after they have started their new lifestyle and return to their original one; therefore, the results are rarely permanent (Curioni and Lourenço, 2005). In the past century, many pharmacons have been approved to support weight loss; however, currently only three APIs and one combination product are available for this indication in the European Union (EU) (Tonstad et al., 2016). Several medicines are no longer available on the market because of safety concerns. Alternative methods are sought-after in the treatment of obesity. The most commonly used products for this purpose are food supplements, which are easily available on the market. However, these products are often counterfeited, containing illegal components. RASFF was set up to aid the national competent authorities in harmonizing their actions and informing one another in the control of food and feed that are posing serious risks (Rapid Alert System for Food and Feed (RASFF), 2020). RASFF is used in the European Union to help obtain the minimally required safety and quality of feed and food (i.e. safety and quality).

The goals of our study were to give an overview on the most widely used natural products, and on the safety profiles of available and withdrawn pharmacons that might be used to facilitate weight loss. We also aimed to assess their presence in food supplements on the European market associated with a warning released by RASFF and to summarize the trends from 1988 to 2019.

PHARMACOTHERAPY OF OBESITY

According to current guidelines, complex measures should be considered in obese patients and pharmacological therapy should only be used along other lifestyle modifications. Actions to address weight management should not only be applied in obese people (BMI ≥30), but also in patients with a BMI ≥27 kg/m^2 if they already have metabolic syndrome or sleep apnea. The efficacy of pharmacotherapy should be assessed and reconsidered within 3 months of initiating the treatment (Yumuk et al., 2015), and it is highly recommended to complete pharmacotherapy with comprehensive lifestyle modifications including calorie deficit and pronounced physical activity.

A great deal of pharmacons previously used in weight management are no longer marketed because of safety issues. These drugs involve amphetamine derivatives, fenfluramine, lorcaserin, phenylpropanolamine, rimonabant, and sibutramine (Bray, 2014; Morris, 2018). The emerged safety concerns highlight that the potential side-effects (CNS-depressing effects, insomnia, toxicity, primary pulmonary hypertension) of pharmacons inducing weight loss should be monitored and assessed more thoroughly (Montan et al., 2019). Currently available medications for this purpose in the European Union are orlistat, liraglutide, naltrexone/bupropion and phentermine resinate (Yumuk et al., 2015; EMA 2020b; The State Institute for Drug Control (SUKL), 2020).

In the meantime, the popularity of food supplements for weight loss management and their market share have been increasing (Ríos-Hoyo and Gutiérrez-Salmeán, 2016). Unfortunately, some products are adulterated with synthetic substances, usually formerly approved weight loss compounds, which had already been withdrawn from the market. Hence, these food supplements can pose serious health risks for consumers.

Medications of Obesity Available in the European Union

Orlistat

Orlistat (1) gained its marketing approval for obesity management by the European Commission (EC) in 1998 (**Supplementary Table S1**). It was the first selective, irreversible inhibitor of gastric and pancreatic lipase enzymes. Its mechanism of action involves the reduction of dietary fat lipolysis and absorption (Al-Suwailem et al., 2006). It is a prescription-only medicine in the European Union. Based on the results of a meta-analysis, orlistat decreased average body weight with 2.35 and 2.94 kg, at doses 60 and 120 mg, respectively (Li et al., 2005). Its use may be associated with clinically relevant mild-to-moderate gastrointestinal adverse effects (e.g. abdominal

pain, diarrhea, fecal spotting, and steatorrhea). Apart from the above-mentioned minor side-effects, serious adverse reactions were also associated with the use of orlistat (e.g. subacute liver failure, cholelithiasis and cholestatic hepatitis). The safety of the chronic use of orlistat is highly questionable because it affects the absorption of other pharmacons and fat-soluble vitamins (Filippatos et al., 2008).

Liraglutide

Liraglutide acts as a glucagon like peptide-1 (GLP-1) receptor agonist and it was first used for the treatment of T2DM (Collins and Costello, 2019). Liraglutide was a promising pharmacon in the therapy of T2DM, because it improved the patients' cardiovascular status and outcome (Marso et al., 2016). After being proved in human studies that GLP-1 analogues promote weight loss, it has become an approved drug for weight management. The mechanism of action of liraglutide involves appetite suppression and delayed gastric emptying (Mehta et al., 2017). Nevertheless, liraglutide was authorized by the European Medicine Agency (EMA) as an adjunct to a comprehensive lifestyle measures to induce weight loss (**Supplementary Table S1**; Christou et al., 2016; EMA, 2020b).

Liraglutide is available as an injection, but another GLP-1 receptor antagonist, semaglutide can be given *per os*. Semaglutide gained its EMA approval recently for the treatment of adults with insufficiently controlled T2DM to improve glycemic control (Gomez-Peralta and Abreu, 2019). Semaglutide is also monitored; therefore, rapid identification of safety concerns and unknown side effects are made possible (EMA, 2020a).

In human studies, the most common side effects associated with the intake of liraglutide included gastrointestinal symptoms (e.g. nausea and vomiting, risk of pancreatitis), and increased pulse rate (Marso et al., 2016). In a clinical trial, from randomization to the 20th week, the mean weight loss in the intention-to-treat (ITT) population, was statistically significantly bigger in the liraglutide treated groups when compared to placebo. The effect was dose-dependent, daily doses of 1.2, 1.8, 2.8, and 3.0 mg liraglutide resulted in a weigh loss of 4.8, 5.5, 6.3, and 7.2 kg, respectively. Taking placebo resulted in a 2.8 kg weigh loss (Astrup et al., 2009).

Naltrexone-Bupropion

After subsequent clinical trials demonstrated its safety, a combination therapy, containing naltrexone (2) and bupropion (3) has been approved in the EU for weight management (**Supplementary Table S1**). Naltrexone acts as an opioid antagonist on the μ-opioid receptor and decreases appetite by inhibiting β-endorphin-mediated autoinhibition of POMC (pro-opiomelanocortin) neurons (Grossman et al., 2003; Cone, 2005; Greenway et al., 2009). The anorectic effects of the antidepressant bupropion is mediated via the stimulation of the activity of POMC cells in the arcuate nucleus of the hypothalamus (Caixàs et al., 2014). Significant weight loss was observed in participants assigned to the combination group after the end of a 56-week-long trial. Patients in the verum group received 32 mg of naltrexone and 360 mg bupropion daily. In groups showing the highest weight loss, the combination was applied for 28–36 weeks, mean change in bodyweight was −6.1 kg (Greenway et al., 2009). Based on the above mentioned evidence, this combination may serve as a possible treatment adjunct to lifestyle modifications by promoting satiety, reducing appetite, enhancing energy expenditure; therefore, it helps patients to achieve weight loss goals (European Medicines Agency, 2015; Sherman et al., 2016). Initially, the first clinical trials focused on the cardiovascular side effects of the combination (Sherman et al., 2016; Tek, 2016). The combination of naltrexone and bupropion is contraindicated in patients with uncontrolled hypertension; however, the possible risks of this combination on cardiometabolic parameters of the patients is not fully understood (Connolly et al., 1997; James et al., 2010). Based on the clinical trials, frequently occurring adverse effects in participants in the verum group were nausea, headache, constipation, dizziness, vomiting, and xerostomia (Vorsanger et al., 2016). Bupropion alone, and in combination with naltrexone increases the blood pressure; therefore, therapies in which bupropion is administered should only be initiated in patients whose blood pressure is well-controlled. Moreover, the patient's blood pressure is to be checked regularly by either the patient itself or by a health care professional throughout the whole course of the treatment.

Phentermine

Phentermine (4) has great potential as a weight loss drug. It also acts on the POMC neurons of the hypothalamus by inhibiting the norepinephrine transporter (Narayanaswami and Dwoskin, 2017). Weigh loss of up to 6 kg have been reported by taking phentermine (15–30 mg/daily) (Lonneman et al., 2013). Phentermine had been used as an approved drug to overcome obesity in Europe since 1956 (**Supplementary Table S1**), and it was a frequently prescribed medicine for decades (Colman, 2005). However, in 2012 the EMA withdraw the marketing authorization of phentermine because of its side-effects. Based on the published evidence, the compound might affect the cardiovascular and the central nervous system when used for a long time. Moreover, the authority was concerned about the possibility of the use of the drug by obese adults for whom taking phentermine may have deteriorating effects (Shin and Gadde, 2013). Nevertheless, phentermine resinate is available in modified-release capsules in the Czech Republic based on the authorization of the national competent authority (The State Institute for Drug Control (SUKL), 2020). Phentermine was combined with topiramate (PHEN/TPM) to achieve weight loss goals and enhance quality of life of obese people. The combination was to be used once daily, but its approval was withdrawn in Europe in 2012, due to concerns regarding its safety (Shin and Gadde, 2013). Although, a 56-week-long trial conducted with a controlled release formulation of phentermine and topiramate (containing 15 mg phentermine and 92 mg topiramate) was proved to have an outstanding efficacy; however, it has to be noted that its use increased dose-dependently the occurrence of psychiatric and cognitive adverse events (Scheen and Van Gaal, 2014).

Withdrawn Amphetamine Derivative-type Medications in the European Union

Amphetamine and its derivates (e.g. phenylpropanolamine, fenfluramine, dexfenfluramine) were used for obesity the first

time in the 1930s (Bray and Greenway, 1999). These compounds are mainly derived from phenylethylamine from which neurotransmitters dopamine, epinephrine and norepinephrine are derived. The weight loss mechanism of action of amphetamine derivatives involves the stimulation of norepinephrine- and dopamine-release in the hypothalamic and limbic regions' satiety centers (Bray, 1993). Amphetamine derivatives exert their anorexigenic effect for a few hours; but tolerance develops relatively fast within only a few weeks. Amphetamine use and abuse often result in cardiac complications (Bazmi et al., 2017). Amphetamine derivatives used as weight loss therapy were removed from the legal market in Europe due to safety concerns and the quick development of tolerance (**Supplementary Table S2**).

Phenylpropanolamine

Phenylpropanolamine (PPA, 5) is available without prescription, and commonly administered as an appetite suppressant for weight loss, and also in cases of cough and common cold (Kernan et al., 2000). PPA is chemically related to the amphetamine-like anorectic agents (Walker et al., 1996). Effects of PPA in weight loss is documented, but the exact mechanism of action is not fully elaborated (Wellman and Sellers, 1986).

Despite the fact that its safety and efficacy profile is controversial, the drug is still available in some European countries. There are safety concerns suggesting a link between the consumption of PPA and stroke (Kernan et al., 2000). In a clinical trial, complementary to a 5,023 kJ (1,200 kcal) diet, patients in the verum group took 75 mg of sustained release PPA for 6 weeks and the achieved weight loss was higher than in the non-treated placebo group (Schteingart, 1992). Patients in the verum group lost 2.59 kg, while the results in the placebo-receiving group was less pronounced (−1.07 kg). 36 patients of the original study were agreed to be enrolled in a further double-blind trial up to 20 weeks, and the difference remained significant (PPA −5.1; placebo −0.4 kg, $p = 0.01$). In spite of the more weight loss in the PPA group, patients did not report a greater anorexigenic effect. The authors of the article concluded that phenylpropanolamine can be used in combination with a diet based on calorie deficit to promote safe weight management.

Fenfluramine, Dexfenfluramine

(+)-Norfenfluramine (6), the active metabolite of prodrugs fenfluramine and dexfenfluramine, induces weight loss and it is a potent agonist on 5-hydroxytryptamine (5-HT_{2C}) receptors (Porter et al., 1999; Fitzgerald et al., 2000). Both drugs, fenfluramine and its (S)-isomer, dexfenfluramine were used in monotherapy, the former one for short-term, and the latter one for long-term weight management, even if its long-term safety was not yet documented (Weintraub et al., 1992). The effects of dexfenfluramine were examined on obese women (n = 52) in a placebo-controlled, double-blind study. Patients in the dexfenfluramine group followed a 1,500 kcal/day diet and took 15 mg dexfenfluramine twice a day (Ditschuneit et al., 1996). After completing the 12-months-long trial, patients in the verum group lost 14.2 ± 2.20 kg, while patients in the placebo group lost only 4.92 ± 2.99 kg. The side-effects of dexfenfluramine are quite alarming though; based on a case-control study, it increased the prevalence of cardiovascular diseases, and its use was associated with pulmonary hypertension (Abenhaim et al., 1996). Therefore, because of safety concerns, both drugs, and the so called fen-phen formulation (combination of fenfluramine and phentermine) were withdrawn from the market in 1997 (Weintraub et al., 1992; Wadden et al., 1998; European Medicines Agency, 2003).

Withdrawn Non-amphetamine Derivative Type Medications in the European Union

2,4-Dinitrophenol

The compound 2,4-dinitrophenol (DNP, **7**) was initially applied in explosive mixtures, but in 1933 it was discovered that DNP causes significant weight loss, and soon it was marketed in slimming products (Tainter et al., 1933). DNP contributes to weigh management by increasing the basal metabolic rate (Cutting et al., 1933). However, serious adverse effects occurred so often that it was withdrawn from the market, and it was labelled as an 'extremely dangerous' drug (**Supplementary Table S3**; Tainter et al., 1934; McFee et al., 2004; Colman, 2007). The side-effects of DNP are associated with its mechanism of action: DNP induces a hyper-metabolic state of the body via uncoupling oxidative phosphorylation, and the excess energy becomes thermal energy in the mitochondria. Hyper-metabolite state is followed therefore with an uncontrolled thermogenesis causing hyperthermia and undesirable elevated body temperature associated with systemic responses (Tainter et al., 1935). After 1938, DNP was no longer prescribed and reports on severe side-effects did not occur, but it is assumed that the use of the compound has not been vanished completely, because case reports of DNP caused deaths still emerged after it has been withdrawn from the legal market (Colman, 2007). Today, DNP is sold illegally as a weight loss aid under a number of different names and its use is encouraged by reports of rapid and safe weight loss (McFee et al., 2004).

Rimonabant

Rimonabant (8), the first antagonist on the cannabinoid receptor type 1 (CB_1-receptor) entered the European market in 2006 (**Supplementary Table S3**) (Rinaldi-Carmona et al., 1995). Initially, it was a promising medication, since several trials proved its effects on weight loss and it also improved several parameters of metabolic syndrome. A meta-analysis of RCTs evaluating the efficacy and safety of rimonabant (20 mg/day) found that the average weight loss in the treated group was 4.7 kg (4.1–5.3 kg), significantly higher, compared to the placebo group (Christensen et al., 2007). However, the use of rimonabant was linked to diverse psychiatric adverse events (e.g. anxiety, depression, and suicidal ideation); therefore, the EMA withdrew the market authorization of rimonabant in the EU in January 2009 (Sam et al., 2011).

Sibutramine

The antidepressant sibutramine (9) inhibits the reuptake of neurotransmitters serotonin (5HT)- and noradrenaline (NA). Apart from its original application later on it was found to

reduce appetite (McNeely and Goa, 1998). In a 12-week-long study, the effects of sibutramine was similar to that of dexfenfluramine. Patients in both groups lost significant amount of weight (4.5 kg, and 3.2 kg, respectively). Sibutramine was used at daily doses ranging from 5 to 30 mg. Based on the results of this study, the optimum daily dose of the drug is 10–15 mg (Lean, 1997). After reports on increased diastolic and systolic blood pressure and pulse rate, concerns were raised regarding the safety of sibutramine (Sharma et al., 2009). Hence, its safety was assessed in the so called Sibutramine Cardiovascular Outcomes Trial (SCOUT) (James, 2005). In this trial the harmlessness of sibutramine was evaluated on patients with a history of cardiovascular disease. As a result, the EMA concluded that the risk-benefit ratio was unfavorable for sibutramine and recommended to suspend all marketing authorizations for sibutramine-containing medicines in Europe (Williams, 2010). Sibutramine was approved in 2001, whereas its market authorization was suspended in 2010 (**Supplementary Table S3**; Ioannides-Demos et al., 2005).

Lorcaserin

Lorcaserin (10), an 5-HT_{2C} receptor agonist, was an approved drug for long-term treatment of obesity and it was intended to be used along with reduced-calorie diet and increased physical activity (Smith et al., 2010). In 2013 (**Supplementary Table S3**), only one year after its marketing approval, the marketing authorization holder officially notified the EMA's Committee for Medicinal Products for Human Use (CHMP) about his wish to withdraw the marketing authorization for lorcaserin, because based on the CHMP' opinion the benefits of lorcaserin—a medicine intended for helping to achieve weight control in obese and overweight patients—did not outweigh its risks (e.g. depression, valvulopathy) (European Medicines Agency, 2013). The weight loss achieved after a one year treatment with lorcaserin ranged from 4.5 to 5.8 kg in the published clinical trials when taking 10 mg lorcaserin once or twice daily (Fidler et al., 2011). Patients taking lorcaserin experienced a significant increased risk of depression (DiNicolantonio et al., 2014). Long-term use might be associated with increased cancer risk (LiverTox, 2012b).

FOOD SUPPLEMENTS FOR WEIGHT LOSS

Considering the limited efficacy and unfavorable side-effect profiles of synthetic drugs, there is a high demand for alternative treatments like herbal products to induce weight loss (Bahmani et al., 2015). One further reason for turning to alternative preparations is the fear from the possible side-effects of synthetic drugs. However, natural origin does not guarantee safety, as it can be demonstrated on the example of ephedrine, a natural alkaloid of species of Ephedraceae having a remarkably high cardiovascular risk (Samenuk et al., 2002). It is a myth that the use of herbal substances are always safe and harmless, and it is important to highlight that herbal compounds can have an interaction with medicines and products of natural origin can cause adverse events as well (Pittler and Ernst, 2001; Dwyer et al., 2005; Poddar et al., 2011; Astell et al., 2013). Moreover, since the regulation and control of food supplements is less strict compared to medicines, the ratio of conterfeit or mislabbelled, potentially dangerous products might be higher.

According to a recent review, most popular natural ingredients marketed for weight management include chitosan, glucomannan, capsaicin, carnitine, and conjugated linoleic acid (CLA) (Wharton et al., 2020). In Europe, other popular herbal ingredients include *Camellia sinensis* (L.) Kuntze (Theaceae), *Garcinia cambogia* (Gaertn.) Desr. (Clusiaceae) and unroasted seed of *Coffea arabica* L. (Rubiaceae) (Barrea et al., 2019; Ríos-Hoyo and Gutiérrez-Salmeán, 2016; The Plant List, 2013). *Hoodia gordonii* (Masson) Sweet ex Decne. (Apocynaceae), *Stevia rebaudiana* (Bertoni) Bertoni (Compositae), *Acaciopsis rigidula* (Benth.) Britton and Rose (Leguminosae family, syn. of *Acacia rigidula*) also occurred frequently as constituent of weight loss products in the warnings of RASFF (The Plant List, 2013). In the following, we present an overview of the most popular ingredients of weight loss products, including some plants that were common constituents of products reported in the RASFF system.

Chitosan

Chitosan, a polysaccharide composed of β-(1→4)-linked D-glucosamine and *N*-acetyl-D-glucosamine units, is formed by the deacetylation of chitin. This compound can be found in the animal kingdom (e.g. the exoskeleton of crustaceans and insects) (Mesa Ospina et al., 2015). It contributes to weight management by lowering the absorption of dietary fat and cholesterol, and it might also promote fat excretion leading to weight loss without dietary modifications (Pokhis et al., 2015). A meta-analysis of 14 RCTs studied the effects of chitosan on body weight, serum lipids and blood pressure (Moraru et al., 2018). The results indicated that by the use of chitosan as a food supplement for up to 52 weeks might promote weight loss (average −1.01 kg). Apart form its slight effects on the body weight, the consumption of chitosan was associated with improvements of serum lipid profile and a significant reduction blood pressure, both systolic and diastolic (−2.68 mmHg, and −2.14 mmHg, respectively).

Based on the published studies, the short-term use of chitosan is safe, but except for those with shellfish allergy (Waibel et al., 2011). Adverse effects include flatulence, constipation, indigestion, nausea, and heartburn (Gallaher et al., 2000). Chitosan might interact with warfarin and partially interferes with the absorption of the fat-soluble vitamins (i.e. vitamins A, D, E, and K); however, its effects on the fecal fat excretion are not fully proven (Huang et al., 2007; Jull et al., 2008).

Glucomannan

The most commonly used type of glucomannan (GM) in weight loss products is extracted from tubers of *Amorphophallus konjac* K. Koch (Araceae) (Xiao et al., 2000, The Plant List, 2013). GM, a hemicellulose-type polysaccharide induces weight loss through several mechanism. It makes the absorption in the small intestine slower; however, reduces the transit time in the small intestine, because it increases the viscosity of the content; furthermore, GM increases energy loss via fecal excretion. GM induces satiety in

several ways: the consumption of GM enhances mastication efforts, and after its consumption it delays gastric emptying; moreover, elevated levels of plasma cholecystokinin induces cephalic– and gastrointestinal-phase satiety signals (Gallaher et al., 2000; Ríos-Hoyo and Gutiérrez-Salmeán, 2016). A meta-analysis found that the daily consumption of GM (1.2–15.1 g/day) for 5 weeks improves the patient' metabolic profile, but only slightly affects the body weight (WMD: −0.79 kg) (Sood et al., 2008). However, contrasting results were reported by Zalewski and Szajewska, 2015, claiming that in otherwise healthy overweight or obese adults, short-term use of GM may promote a slight weight loss, but it does not affect the BMI. The effects of GM on children are not enough to establish a firm conclusion. Mild gastrointestinal adverse effects (bloating, diarrhea) were associated with the use of GM (Keithley and Swanson, 2005).

Capsaicin

Capsaicin (11) and capsaicinoids are agonists of the TRPV1 (transient receptor potential vanilloid subfamily 1) receptor, and they mimic the effects of cold, which decreases the fat mass through the activation and recruitment of brown adipose tissue (Saito, 2015). Capsaicin affects the oxidation of lipid and influences energy expenditure (Whiting al., 2014; Ludy et al., 2012; Zheng et al., 2017). Food rich in capsaicin contributes to weight management by preventing obesity (Zheng et al., 2017). There are also reports that the body weight of healthy women who regularly use chili peppers is slightly reduced when compared to those who do not use chili (Henry and Emery, 1986; Yoshioka et al., 1998). A meta-analysis based on eight studies involving 191 participants concluded that patients who took 2 mg capsaicin before each meal consumed less calorie by an average of 74 kcal; therefore, capsaicin may help maintain weight by reducing total energy intake (Whiting et al., 2014). However, based on other literature data, the level of its effects on thermogenesis and fat oxidation is moderate and its long-term efficacy is questionable (Lejeune et al., 2003). A middle-aged man with normal BMI would lose approximately 0.5 kg over 6.5 years if he pursued a calorie deficit diet of 10 kcal and consumed hedonically acceptable doses of capsaicin (Ludy et al., 2012), whereas a weight loss of 2.6 kg over 8.5 years would be reachable if he was in a 50 kcal negative energy balance (Galgani and Ravussin, 2010; Hall, 2010). Capsaicin at acceptable doses is safe, although it might cause mild-to-moderate gastrointestinal side-effects, sweating, flushing, and rhinorrhea (Avesaat et al., 2016). In addition, capsaicin compounds can interfere with antihypertensive agents (Patanè et al., 2010).

Carnitine

Carnitine (12) transports long-chain fatty acids (FAs) into the mitochondria for transformation, and energy is produced from these FAs via β-oxidation, and it also aids eliminate toxic compounds from the cell (NIH, 2017). L-carnitine is the isomer of carnitine that is used to enhance weight loss (Elmslie et al., 2006). Nine RCTs involving 911 patients were summed up and analyzed in a systematic review and meta-analysis (Pooyandjoo et al., 2016). Participants receiving carnitine (in doses varying from 1.8 g/day to 4 g/day) lost significantly more weight (−1.33 kg) and their BMI decreased significantly more (−0.47 kg/m^2) than patients receiving the control treatment. The results revealed that the weight loss effects of carnitine diminished over time. L-carnitine is very well tolerated; at doses of up to 15 g daily and there were only a few, mild side effects like infrequent diarrhea, gastralgia and nausea (Goa and Brogden, 1987).

Conjugated Linoleic Acid

Conjugated linoleic acid (CLA) and its isomers activate different nuclear receptors and, thus, they differentially regulate the expression of those genes that are related to lipid metabolism (Chin et al., 1994). The natural sources of are beef meat and dairy products, but it can also be found in dietary supplements (Schmid et al., 2006). A meta-analysis of human studies indicated that the effect of CLA on weight loss was superior to that of the placebo: median doses of 3.2 g was effective and reduced fat mass (Whigham et al., 2007). However, in certain studies, the association between CLA and weight loss was not observed (Wharton et al., 2020). Nevertheless, there is a clear need for further, larger human trials assessing the efficacy and safety of CLA dietary supplements (Whigham et al., 2004). In animal studies CLA interfered with glucose metabolism (e.g. increased insulin resistance in mice) and lead to a change in liver function inducing lipodystrophy; therefore, these effects should be evaluated in human studies as well to rule out any safety concerns (Clément et al., 2002).

Green Coffee

Unroasted seed of *Coffea arabica* L. are good sources of chlorogenic acids (13) that are not present in roasted coffee because of their thermolability (Farah et al., 2008). The possible use of green coffee in weight management is related to its chlorogenic acid content (Shimoda et al., 2006). Chlorogenic acid-rich green coffee extracts reduce blood lipid and glucose levels, blood pressure, and reduce the risk of certain cardiovascular diseases (Sanlier et al., 2019). A meta-analysis of three RCTs involving a total of 142 participants revealed that by the consumption of green coffee extract (GCE) a significant reduction in body weight was achieved (Onakpoya et al., 2011b). The authors of the above-mentioned meta-analysis could not establish an effective dose for the extract. The grade of evidence of this analysis is moderate, and if more rigorous trials with longer duration are published, the efficacy and safety of GCE in weight management might become appraisable.

Green Tea

The non-fermented leaves of *Camellia sinensis* (L.) Kuntze is green tea. Its main active compounds are catechin polyphenols, such as epicatechin, epigallocatechin, epicatechin-3-gallate and epigallocatechin-3-gallate (EGCG, 14). From these constituents, EGCG is the one in which green tea is the most abundant and this compound is the most important with respect to its pharmacological effects (Musial et al., 2020). Caffeine is also a major pharmacologically active ingredient of green tea (Jeukendrup and Randell, 2011). It was found that a

combination of green tea and caffeine contributed to weight management in people who usually consume low amounts of caffeine. The effect was attributed to enhanced thermogenesis and fat oxidation (Dulloo et al., 1999). This might be explained by the caffeine content of tea, since high doses of caffeine elevates thermogenesis and fat oxidation and lowers leptin levels; therefore, it might have body weight reducing effects (Westerterp-plantenga et al., 2005). Moreover, catechins, especially EGCG, inhibits catechol-*O*-methyltransferase (COMT) and therefore enhances fat oxidation (Westerterp-plantenga et al., 2005). A meta-analysis of human studies carried out with green tea proved that EGCG-containing extracts have significant effect on weight loss and its maintenance (WMD: −1.31 kg; duration at least 12 weeks). When analyzing the data from studies in which high regular caffeine intake was recorded, the effect of caffeine intake on body weight was not significant. However, the studied population differed in these two groups, i.e. low caffeine intake was studied on Asian participants and moderate-to-high caffeine doses were studied in Caucasian people; therefore, the conflicting results might derive form the heterogeneity of the included studies (Hursel et al., 2009). Green tea extracts are common constituents of slimming products; however, there are concerns about the hepatotoxicity of extracts with high (>100 mg/day) EGCG content (Oketch-Rabah et al., 2020).

Garcinia cambogia

The main acid compound of *Garcinia cambogia* (Gaertn.) Desr. is (-)-Hydroxycitric acid (HCA, 15). This compound have proven adenosine triphosphate (ATP) citrate lyase inhibitory effects (Watson et al., 1969). The inhibition of the above mentioned enzyme restricts the availability of acetyl coenzyme A (acetyl-CoA) units that are necessary for fatty acid synthesis and lipogenesis during a so called lipogenic diet when patients consume high amounts of carbohydrates (Kornacker and Lowenstein, 1965; Bressler and Brendel, 1966; Linn and Srere, 1979). The compound restrains the synthesis of FAs, lipogenesis, appetite, and therefore aids weight loss (Sullivan et al., 1972). Despite its promising mechanisms, clinical studies have shown controversial findings (Jena et al., 2002). Nine RCTs were analyzed in a meta-analysis which revealed a small but significant weight loss promoting effect of HCA when compared to placebo (Onakpoya et al., 2011a). The duration of the included studies varied from 2 to 12 weeks, and the participants took 1–2.8 g of HCA daily. More recently, cases of acute liver injury have been emerged in association with a product claimed to contain *Garcinia cambogia*. It is alarming that not only mild side effects (transient and moderate enzyme elevations) were reported but symptomatic acute hepatitis and acute liver failure were also described (LiverTox, 2012a). The frequency of hepatic adverse reactions is not known but it seems to be uncommon (<1:10,000). HCA might influence glucose homeostasis by modifying insulin sensitivity, and increasing gluconeogenesis and the formation of ketone bodies (McCarty and Majeed, 1994; Jena et al., 2002).

Hoodia gordonii

The consumption of *Hoodia gordonii* (Masson) Sweet ex Decne. has its tradition among a native South African people (van Heerden, 2008). Bushmen used to eat this succulent plant for its appetite reducing effects. In Europe, *H. gordonii* can only be marketed after appropriate safety assessment, since it was not used as a food or food ingredient before 15 May 1997 (European Commission, 2020). An oxypregnane glycoside, P57 (16) is assumed to be responsible for the appetite reducing effects of *H. gordonii*. It was found that after intracerebroventricular administration, P57 increased ATP production in the hypothalamus (MacLean and Luo, 2004). No published, peer-reviewed meta-analysis of RCTs examining the efficacy of *Hoodia* were found in the literature (PubMed/Medline, the Cochrane Library, ClinicalKey and Google Scholar). In a placebo-controlled study involving overweight women, the weight loss efficacy of *H. gordonii* was compared to placebo. Participants were classified by body fat percentages, and 25 of them took *H. gordonii* and 24 received placebo (Blom et al., 2011). To ensure identical circumstances for each participant during the 15-day-long study, they stayed in the clinic 4 days prior to the study for a run-in period and during the 15-days treatment period. Participants were asked to consume a yogurt drink 1 h prior to each breakfast and dinner. The yogurt contained 1,110 mg *H. gordonii* or placebo. There were no serious adverse events but nausea, vomiting, and disturbances of skin sensation occurred in the verum group. Blood pressure, pulse rate, bilirubin and alkaline phosphatase levels increased significantly in the verum group. Recently alarming side effects (elevated blood pressure and heart rate) that are in line with the previously describe study have been reported (Roza et al., 2013).

Stevia rebaudiana

The plant *Stevia rebaudiana* (Bertoni) Bertoni is native to South America, and Native Americans used it for centuries to sweeten their food and also for medicinal purposes, as herbal tea to alleviate several ailments, such as heartburn (Lemus-Mondaca et al., 2012). Glucosides obtained from *S. rebaudiana* are approximately 300 times sweeter than sucrose. Nowadays, when obesity has become a worldwide problem, low- and no-calorie sweeteners, such as *S. rebaudiana* offers an alternative that might help reduce sugar intake, and decrease the incidence of diseases derived from high refined sugar consumption (Samuel et al., 2018).

The whole plant and also the dried leaves of *S. rebaudiana* are novel foods in the EU based on the Regulation (EC) No 258/97 (European Commission, 1997). Extracts prepared from the leaves of *S. rebaudiana* are authorized as novel food, based on the Regulation (EC) No 1333/2008 on food additives or Regulation (EC) No 1334/2008 on flavorings, respectively (European Commission, 2008). The regulation covers only herbal tea containing or prepared with leaves of *S. rebaudiana* and preparations that are to be used for sweetening or flavoring purposes, every other use of *Stevia* is still unauthorized in the European Union.

S. rebaudiana appears to be safe. Human and animal studies have shown that steviol glycosides do not possess nor carcinogenic, nor mutagenic, nor teratogenic activates, and they do not have acute or subacute toxicity (Momtazi-Borojeni et al., 2017).

Acacia rigidula

Extracts of *Acaciopsis rigidula* (Benth.) Britton and Rose leaves are used in weight loss products with little or no published clinical data about their potential biological effects, and has no documented history of use as food or traditional herbal treatment (Pawar et al., 2014). A comprehensive literature search in several databases (PubMed/Medline, the Cochrane Library, ClinicalKey and Google Scholar) yielded no results regarding its safety and efficacy. The consumption of *A. rigidula* might be dangerous because it contains appreciable amounts of toxic azotoids (Clement et al., 1998). *A. rigidula* is still not a novel food in the European Union, hence it cannot be market as food supplement, only taxons *Acacia arabica* (Lam.) Willd., *Acacia nilotica*(L.) Delile, *Acacia senegal* (L.) Willd. *and Acacia verek* Guill. and Perr. are authorized as a novel food ingredient (European Commission, 2020).

MATERIALS AND METHODS

Retrospective data were extracted from the RASFF portal. Data from individual warnings were recorded (date, product, product category, notification type, countries concerned, subject, action taken, distribution status and risk decision). Records were grouped into four main categories:

(1) "A" for unauthorized ingredients;
(2) "B" for unsafe ingredients;
(3) "C" if there was a problem with the level of the ingredient (too high or too low);
(4) "D" other problems (eg mislabeling, taste disturbance).

RASFF signals are classified as alert, information notification or border rejection as part of its RASFF Portal. Subcategories were created based on the intended use of the reported product. The risks and adverse effects were also assessed. Data from 1988 to 2019 were extracted from the reported supplements database on January 1, 2020. Each entry was individually reviewed. After the data set was categorized, descriptive analyses were performed using Microsoft Excel 2010 (Microsoft Excel, RRID:SCR_016137) for Windows (Microsoft Inc.).

RESULTS

The raw data set from the RASFF database included 2,559 records of food supplements with quality problems and several of these products were marketed to facilitate weight loss [319 (12.5%)]. 202 (63.3%) of these slimming products contained unapproved, synthetic weight loss pharmacons. Other frequently used adulterants were erectile dysfunction drugs and performance-enhancers which are not included in this article.

The overall reports extracted from RASFF show that the first notifications were created in 2003, and the number of the reported signals kept growing until 2019 (especially in case of DNP). The majority of the adulterated anti-obesity products contained DNP (113 of 319, 35.4%). Sibutramine was the second most frequent adulterant (69 products, 21.6%) in the weight loss food supplement category and it was reported in almost every year, in contrast with DNP, which was reported only in four different years, in 2003, 2017, 2018, 2019. Phenolphthalein, a laxative with genotoxic and carcinogenic potential was the less common synthetic adulterant, with 20 reports. Unauthorized plant ingredients such as *Hoodia gordonii* (Masson) Sweet ex Decne., *Stevia rebaudiana* (Bertoni) Bertoni, and *Acaciopsis rigidula* (Benth.) Britton and Rose (in RASFF portal recorded as syn.: *Acacia rigidula*) were reported less frequently (**Figure 1**).

Based on our statistical overview, adulterated DNP products have been reported mainly in the United Kingdom. Whereas sibutramine has been reported with the highest number in Germany followed by Cyprus and Slovenia, it was reported less frequently in other countries (**Supplementary Figure S1**).

Based on the reports, DNP as adulterant first appeared in 2003, in Finland, and there were no reports on DNP until 2017, and then in 2017, it appeared again, and the number of DNP-containing products started to increase dramatically. The notifications originated from the United Kingdom and Cyprus.

Sibutramine was first detected in food supplements in the 2005, and since then it is a common adulterant in the EU. The number of reports on sibutramine-containing products peaked in 2012 (21 reports) and concerned many countries in the EU. The first 2 phenolphthalein reports originated from Hungary and Cyprus. The maximum number of phenolphthalein was seven reports in 2013 from Germany (**Supplementary Table S4**).

The ratio of the emergence of these three, commonly used synthetic compounds can be seen in **Supplementary Figure S2**. Based on the reports, it can be concluded that sibutramine emerged more frequently, but it occurred in fewer products. DNP was mainly present in 2018 (41 times) and in 2019 (70 times), while the popularity of sibutramine seemingly peaked in the early 2010s, in 2011 and 2012 14 and 21 reports were registered, respectively. Phenolphthalein emerged with the highest reports in 2012 with six reports and with seven reports in 2013.

Based on the RASFF signals *Hoodia gordonii* [66 of 117 (56.4%)], Stevia rebaudiana [23 (19.66%)] and *Acacia rigidula* [28 (23.93%)] were reported as unauthorized herbal products. The countries affected by adulterated products were Poland, Lithuania, France, Malta, Spain, Belgium, Austria, Switzerland, Ireland, Sweden, and Finland as shown in **Supplementary Figure S3**.

Hoodia gordonii was reported for the first time, in 2005 in the Netherlands (2 reports). The greatest number of products containing *Hoodia goordonii* was reported in 2017 (30 reports). In 2016, there were no reports on *Hoodia gordonii*. The first appearance of a product containing unauthorized *Stevia rebaudiana* was reported in Denmark in 2006. The highest number of reports on products containing unathorized *Stevia rebaudiana* was four in 2010. Except for 2005, 2015, 2018, 2019, it was present in every year from 1988–2019. *Acacia rigidula* was first reported in 2016, firstly in the Netherlands, but later also in Belgium, Austria, France, Malta, Spain and other European countries, overall 28 records were found in RASFF (**Supplementary Table S5**).

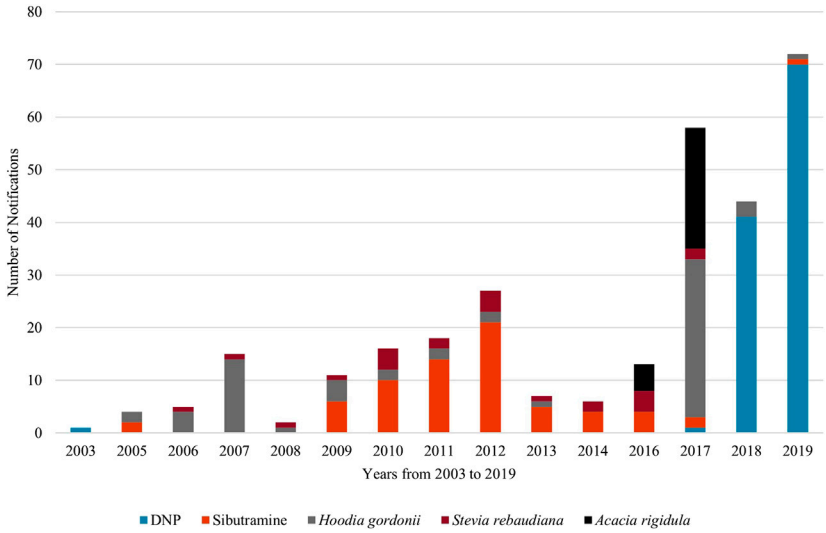


FIGURE 1 | Notifications on weight loss food supplements in the RASFF (2003–2019).

The ratio of these three reported, natural products with safety concerns are represented in **Supplementary Figure S4**. *Hoodia gordonii* was present more often, in smaller quantities, with the highest occurrence of 30 reports in 2017. *Stevia rebaudiana* has been reported in almost every year, but the highest number of reports was only four. The appearance of *Acacia rigidula* only started at 2016 and it emerged again in 2017 with 23 records.

DISCUSSION

The aim of our work was to summarize the trends concerning adulterated food supplements associated with a warning released by the RASFF between 1988 and 2019, focusing on products with intended use as slimming agent. RASFF is a platform for reporting food safety issues within the European Union. When a RASFF member suspects that a food or feed poses a serious risk to the people's health, the member state should notify the European Commission (EC) via RASFF without any delay. In cases of withdrawing or recalling products from their market or in cases when rapid measures are needed, the members are obliged to notify the EC to help protect peoples' health.

The increasing number of signals on illegal food supplements in RASFF reveals that the presence of undeclared ingredients poses an important public health concern. Illegal supplements marketed for weight loss were most commonly adulterated with DNP or sibutramine between 1988 and 2019. The use of former one may result in quick weight loss, but often causes serious adverse events (Colman, 2007). Several deaths attributable to DNP have been published (Cann and Verhulst, 1960). DNP was detected as an adulterant for the first time in 2003, but the number of products containing this compound has been increasing from 2017 through 2019, reported mainly in the United Kingdom. Sibutramine was reported in several countries; however, the number of products containing sibutramine was lower. SCOUT confirmed that sibutramine (at daily doses ranging from 10 to 15 mg) increases the risk for nonfatal myocardial infarction and nonfatal stroke in patients with preexisting cardiovascular disease, and have an increased potential to develop high blood pressure or pulse rate (Sharma et al., 2009).

It is alarming that the majority of the reported signals were in connection with unsafe synthetic substances. There have been increasing number of reports on DNP, and since this substance can cause serious side effects it is necessary to monitor the use of DNP more closely in the future.

Out of the most popular food supplements with natural origin the extracted materials of *Hoodia gordonii* (Masson) Sweet ex Decne., *Stevia rebaudiana* (Bertoni) Bertoni, and *Acaciopsis rigidula* (Benth.) Britton and Rose were unauthorized products registered in RASFF from 1988–2019. *Stevia rebaudiana* seems to be the least dangerous component based on the reports of our review on RASFF. It was reported in small quantity, and for now became authorized as a novel food according to EC Regulation EC No. 258/97 (European Commission, 1997). In spite of that it has been traditionally used for hundreds of years, more scientific and clinical studies are needed to verify its safety, because it was represented almost in every year in RASFF from 1988–2019, and it is very popular among the consumers.

The other two plants (*H. gordonii*, *A. rigidula*) are still not authorized as a novel food and their safety is not scientifically proven (Roza et al., 2013; Clement et al., 1998).

Despite the fact that *H. gordonii* is often used as an adulterant, and advertised for its weight loss promoting effects, there is still little known about its chemical constituents and their mechanism of action. Recent research suggests that the use *H. gordonii* may cause increased blood pressure and pulse rate (Roza et al., 2013). Taken into consideration that *H. gordonii* emerges regularly from 1988, it would be important to monitor food supplements containing *Hoodia*.

A. rigidula is a shrub native to the Southeastern United States, and it contains several biogenic amines. The plant has been marked in products promoting weigh loss; however, its effects are not yet supported by either its traditional usage, since it has never been used in the traditional medicine, or by research results. *Acacia rigidula* occurred in the RASFF portal recently, the presence of *A. rigidula* should be monitored closely in weight loss dietary supplements.

CONCLUSION

As several medications used to manage body weight are no longer available on the market, because of their serious adverse effects; there is a clear need for effective products to support weight loss because currently there are only a few therapeutic options to address this issue. However, the efficacy of natural ingredients usually does not meet the customers' expectations.

Some products (typically sold as food supplements) are adulterated with synthetic compounds to increase their efficacy. Adulterated food supplements may cause serious adverse effects, and their interactions with other medicines are also unpredictable. Therefore, it is alarming that the number of signals on adulterated products in RASFF is increasing. As the food supplement industry continues to grow worldwide, it is important to mark these signals as a public health issue, and to elaborate various measures to decrease the number of these signals by improving the safety, quality and testing of food supplements.

AUTHOR CONTRIBUTIONS

DK. collected and analyzed the data and drafted the manuscript. BT and OR. analyzed the data and checked the manuscript for validity. DC. conceptualized the research and did the final check of the manucsript.

FUNDING

The financial support of University of Szeged Open Access Fund is acknowledged.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2020.611361/full#supplementary-material.

REFERENCES

Abenhaim, L., Moride, Y., Brenot, F., Rich, S., Benichou, J., Kurz, X., et al. (1996). Appetite-suppressant drugs and the risk of primary pulmonary hypertension. International primary pulmonary hypertension study group. *N. Engl. J. Med.* 335, 609–616. doi:10.1056/NEJM199608293350901

Al-Suwailem, A., Al-Tamimi, A., Al-Omar, M., and Al-Suhibani, M. (2006). Safety and mechanism of action of orlistat (tetrahydrolipstatin) as the first local antiobesity drug. *J. Appl. Sci. Res.* 2, 205–208.

Astell, K. J., Mathai, M. L., and Su, X. Q. (2013). Plant extracts with appetite suppressing properties for body weight control: a systematic review of double blind randomized controlled clinical trials. *Compl. Ther. Med.* 21, 407–416. doi:10.1016/j.ctim.2013.05.007

Astrup, A., Rössner, S., Van Gaal, L., Rissanen, A., Niskanen, L., Al Hakim, M., et al. (2009). Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. *Lancet*. 374, 1606–1616. doi:10.1016/S0140-6736(09)61375-1

Avesaat, M. Van, Troost, F. J., Westerterp-plantenga, M. S., Helyes, Z., Le Roux, C. W., Dekker, J., et al. (2016). Capsaicin-induced satiety is associated with gastrointestinal distress but not with the release of satiety hormones. *Am. J. Clin. Nutr.* 103 (2), 305–313. doi:10.3945/ajcn.115.123414.1

Bahmani, M., Eftekhari, Z., Saki, K., Fazeli-Moghadam, E., Jelodari, M., and Rafieian-Kopaei, M. (2015). Obesity phytotherapy: review of native herbs used in traditional medicine for obesity. *J Evid Based Complementary Altern Med.* 21, 228–234. doi:10.1177/2156587215599105

Barness, L. A., Opitz, J. M., and Gilbert-Barness, E. (2007). Obesity: genetic, molecular, and environmental aspects. *Am. J. Med. Genet.* 143A, 3016–3034. doi:10.1002/ajmg.a.32035

Barrea, L., Altieri, B., Polese, B., De Conno, B., Muscogiuri, G., Colao, A., et al. (2019). Nutritionist and obesity: brief overview on efficacy, safety, and drug interactions of the main weight-loss dietary supplements. *Int. J. Obes. Suppl.* 9, 32–49. doi:10.1038/s41367-019-0007-3

Bazmi, E., Mousavi, F., Giahchin, L., Mokhtari, T., and Behnoush, B. (2017). Cardiovascular complications of acute amphetamine abuse: cross-sectional study. *Sultan Qaboos Univ. Med. J.* 17, e31–e37. doi:10.18295/squmj.2016.17.01.007

Blom, W. A., Abrahamse, S. L., Bradford, R., Duchateau, G. S., Theis, W., Orsi, A., et al. (2011). Effects of 15-d repeated consumption of Hoodia gordonii purified extract on safety, ad libitum energy intake, and body weight in healthy, overweight women: a randomized controlled trial. *Am. J. Clin. Nutr.* 94, 1171–1181. doi:10.3945/ajcn.111.020321

Bray, G. A., and Greenway, F. L. (1999). Current and potential drugs for treatment of obesity. *Endocr. Rev.* 20, 805–875. doi:10.1210/edrv.20.6.0383

Bray, G. A. (1993). Use and abuse of appetite-suppressant drugs in the treatment of obesity. *Ann. Intern. Med.* 119, 707–713. doi:10.7326/0003-4819-119-7-part-2-199310011-00016

Bray, G. A. (2014). Medical treatment of obesity: the past, the present and the future. *Best Pract. Res. Clin. Gastroenterol.* 28, 665–684. doi:10.1016/j.bpg.2014.07.015

Bressler, R., and Brendel, K. (1966). The role of carnitine and carnitine acyltransferase in biological acetylations and fatty acid synthesis. *J. Biol. Chem.* 241, 4092–4097.

Caixàs, A., Albert, L., Capel, I., and Rigla, M. (2014). Naltrexone sustained-release/bupropion sustained-release for the management of obesity: review of the data to date. *Drug Des. Dev. Ther.* 8, 1419–1427. doi:10.2147/DDDT.S55587

Cann, H. M., and Verhulst, H. L. (1960). Fatality from acute dinitrophenol derivative poisoning. *Am. J. Dis. Child.* 100, 947–948. doi:10.1001/archpedi.1960.04020040949024

Chin, S. F., Storkson, J. M., Albright, K. J., Cook, M. E., and Pariza, M. W. (1994). Conjugated linoleic acid is a growth factor for rats as shown by enhanced weight gain and improved feed efficiency. *J. Nutr.* 124, 2344–2349. doi:10.1093/jn/124.12.344

Christensen, R., Kristensen, P. K., Bartels, E. M., Bliddal, H., and Astrup, A. (2007). Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials. *Lancet.* 370, 1706–1713. doi:10.1016/S0140-6736(07)61721-8

Christou, G. A., Katsiki, N., and Kiortsis, D. N. (2016). The current role of liraglutide in the pharmacotherapy of obesity. *Curr. Vasc. Pharmacol.* 14, 201–207. doi:10.2174/1570161113666150615111951

Clement, B. A., Goff, C. M., and Forbes, T. D. A. (1998). Toxic amines and alkaloids from Acacia rigidula. *Phytochemistry*. 49, 1377–1380. doi:10.1016/S0031-9422(97)01022-4

Clément, L., Poirier, H., Niot, I., Bocher, V., Guerre-millo, M., Krief, S., et al. (2002). Dietary trans-10,cis-12 conjugated linoleic acid induces hyperinsulinemia and fatty liver in the mouse, *J. Lipid Res*. 43, 1400. doi:10.1194/jlr.M20008-JLR200

Collins, L., and Costello, R. A. (2019). *Glucagon-like peptide-1 receptor agonists. St. Bernards medical center*., Treasure Island: StatPearls Publishing.

Colman, E. (2005). Anorectics on trial: a half century of federal regulation of prescription appetite suppressants. *Ann. Intern. Med*. 143 (5), 380–5. doi:10.7326/0003-4819-143-5-200509060-00013

Colman, E. (2007). Dinitrophenol and obesity: an early twentieth-century regulatory dilemma. *Regul. Toxicol. Pharmacol*. 48, 115–117. doi:10.1016/j.yrtph.2007.03.006

Cone, R. D. (2005). Anatomy and regulation of the central melanocortin system. *Nat. Neurosci*. 8, 571–578. doi:10.1038/nn1455

Connolly, H. M., Crary, J. L., McGoon, M. D., Hensrud, D. D., Edwards, B. S., Edwards, W. D., et al. (1997). Valvular heart disease associated with fenfluramine-phentermine. *N. Engl. J. Med*. 337, 581–588. doi:10.1056/NEJM199708283370901

Curioni, C. C., and Lourenço, P. M. (2005). Long-term weight loss after diet and exercise: a systematic review. *Int. J. Obes*. 29, 1168–1174. doi:10.1038/sj.ijo.0803015

Cutting, W. C., Mehrtens, H. G., and Tainter, M. L. (1933). Actions and uses of dinitrophenol: promising metabolic applications. *J. Am. Med. Assoc*. 101, 193–195. doi:10.1001/jama.1933.02740280013006

DiNicolantonio, J. J., Chatterjee, S., O'Keefe, J. H., and Meier, P. (2014). Lorcaserin for the treatment of obesity? A closer look at its side effects. *Open Heart*. 1, e000173. doi:10.1136/openhrt-2014-000173

Ditschuneit, H. H., Flechtner-Mors, M., and Adler, G. (1996). The effects of dexfenfluramine on weight loss and cardiovascular risk factors in female patients with upper and lower body obesity. *J. Cardiovasc. Risk*. 3, 397–403. doi:10.1177/174182679600300411

Dulloo, A. G., Duret, C., Rohrer, D., Girardier, L., Mensi, N., Fathi, M., et al. (1999). Efficacy of a green tea extract rich in catechin polyphenols and caffeine in increasing 24-h energy expenditure and fat oxidation in humans. *Am. J. Clin. Nutr*. 70, 1040–1045. doi:10.1093/ajcn/70.6.1040

Vandermander, J. T., Allison, D. B., and Coates, P. M. (2005). Dietary supplements in weight reduction. *J. Am. Diet Assoc*. 105, S80–S86. doi:10.1016/j.jada.2005.02.028

Elmslie, J. L., Porter, R. J., Joyce, P. R., Hunt, P. J., and Mann, J. I. (2006). Carnitine does not improve weight loss outcomes in valproate-treated bipolar patients consuming an energy-restricted, low-fat diet. *Bipolar Disord*. 8, 503–507. doi:10.1111/j.1399-5618.2006.00345.x

European Commission (1997). The European parliament and the council of the European union. 1997 regulation (EC) no 258/97 of the European parliament and of the council of 27 January1991 concerning novel foods and novel food ingredients. *Off. J. Eur. Union. L*. 43, 1–6.

European Commission (2008). The European parliament and the council of the European Union. Regulation (EC) No 1334/2008 of the European parliament and of the council of 16 December 2008 on flavourings and certain food ingredients with flavouring properties for use in and on foods and amending Council Regulation (EEC) No 1601/91, Regulations (EC) No 2232/96 And (EC) No 110/2008 and directive 2000/13/EC. *Off. J. Eur. Union. L*. 354/34, 34–50.

European Commission (2020). EU Novel food catalogue (v.1.1). Available at: https://ec.europa.eu/food/safety/novel_food/catalogue/search/public/?event=home&seqfce=234&ascii=O (Accessed August 10, 2020).

European Medicines Agency (2003). The European agency for the evaluation of medicinal products (EMEA) patients' working group. *React. Wkly. NA*. 2, 2. doi:10.2165/00128415-200309530-00002

European Medicines Agency (2013). Withdrawal of the marketing authorisation application for Belviq (lorcaserin). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2013/05/WC500143811.pdf (Accessed August 10, 2020).

European Medicines Agency (2020a). First Oral GLP-1 Treatment for Type 2 Diabetes Recommended by EMA. Available at: https://www.ema.europa.eu/en/news/first-oral-glp-1-treatment-type-2-diabetes (Accessed August 13, 2020).

European Medicines Agency (2020b). Medicines. Available at: https://www.ema.europa.eu/en/medicines (Accessed October 15, 2020).

European Medicines Agency (2015). Mysimba-procedural steps taken and scientific information after the authorisation. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/mysimba (Accessed August 10, 2020).

Farah, A., Monteiro, M., Donangelo, C. M., and Lafay, S. (2008). Chlorogenic acids from green coffee extract are highly bioavailable in humans. *J. Nutr*. 138, 2309–2315. doi:10.3945/jn.108.095554

Fidler, M. C., Sanchez, M., Raether, B., Weissman, N. J., Smith, S. R., Shanahan, W. R., et al. (2011). A one-year randomized trial of lorcaserin for weight loss in obese and overweight Adults: the BLOSSOM trial. *J. Clin. Endocrinol. Metab*. 96, 3067–3077. doi:10.1210/jc.2011-1256

Filippato, T., Derdemezis, C., Gazi, I., Nakou, E., Mikhailidis, D., and Elisaf, M. (2008). Orlistat-associated adverse effects and drug interactions: a critical review. *Drug Saf*. 31, 53–65. doi:10.2165/00002018-200831010-00005

Finucane, M. M., Stevens, G. A., Cowan, M. J., Danaei, G., Lin, J. K., Paciorek, C. J., et al. (2011). National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9·1 million participants. *Lancet*. 377, 557–567. doi:10.1016/S0140-6736(10)62037-5

Fitzgerald, L. W., Burn, T. C., Brown, B. S., Patterson, J. P., Corjay, M. H., Valentine, P. A., et al. (2000). Possible role of valvular serotonin 5-HT(2B) receptors in the cardiopathy associated with fenfluramine. *Mol. Pharmacol*. 57, 75–81.

Galgani, J. E., and Ravussin, E. (2010). Effect of dihydrocapsiate on resting metabolic rate in humans. *Am. J. Clin. Nutr*. 92, 1089–1093. doi:10.3945/ajcn.2010.30036

Gallaher, C. M., Munion, J., Hesslink, R., Wise, J., and Gallaher, D. D. (2000). Cholesterol reduction by glucomannan and chitosan is mediated by changes in cholesterol absorption and bile acid and fat excretion in rats. *J. Nutr*. 130, 2753–2759. doi:10.1093/jn/130.11.2753

Goa, K. L., and Brogden, R. N. (1987). l-Carnitine. A preliminary review of its pharmacokinetics, and its therapeutic use in ischaemic cardiac disease and primary and secondary carnitine deficiencies in relationship to its role in fatty acid metabolism. *Drugs*. 34, 1–24. doi:10.2165/00003495-198734010-00001

Gomez-Peralta, F., and Abreu, C. (2019). Profile of semaglutide in the management of type 2 diabetes: design, development, and place in therapy. *Drug Des. Dev. Ther*. 13, 731–738. doi:10.2147/DDDT.S165372

Greenway, F. L., Dunayevich, E., Tollefson, G., Erickson, J., Guttadauria, M., Fujioka, K., et al. (2009). Comparison of combined bupropion and naltrexone therapy for obesity with monotherapy and placebo. *J. Clin. Endocrinol. Metab*. 94, 4898–4906. doi: doi:10.1210/jc.2009-1350

Grossman, H. C., Hadjimarkou, M. M., Silva, R. M., Giraudo, S. Q., and Bodnar, R. J. (2003). Interrelationships between mu opioid and melanocortin receptors in mediating food intake in rats. *Brain Res*. 991, 240–244. doi:10.1016/S0006-8993(03)03442-5

Hall, K. D. (2010). Mechanisms of metabolic fuel selection: modeling human metabolism and body-weight change. *IEEE Eng. Med. Biol. Mag*. 29, 36–41. doi:10.1109/MEMB.2009.935465

Henry, C. J., and Emery, B. (1986). Effect of spiced food on metabolic rate. *Hum. Nutr. Clin. Nutr*. 40, 165–8Refstyled.

Huang, S. S., Sung, S. H., and Chiang, C. E. (2007). Chitosan potentiation of warfarin effect. *Ann. Pharmacother*. 41, 1912–1914. doi:10.1345/aph.1K173

Hursel, R., Viechtbauer, W., and Westerterp-Plantenga, M. S. (2009). The effects of green tea on weight loss and weight maintenance: a meta-analysis. *Int. J. Obes*. 33, 956–961. doi:10.1038/ijo.2009.135

Ioannides-Demos, L. L., Proietto, J., and McNeil, J. J. (2005). Pharmacotherapy for obesity. *Drugs*. 65, 1391–1418. doi:10.2165/00003495-200565100-00006

James, W. P., Caterson, I. D., Coutinho, W., Finer, N., Van Gaal, L. F., Maggioni, A. P., et al. (2010). Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. *N. Engl. J. Med*. 363, 905–917. doi:10.1056/NEJMoa1003114

James, W. P. T. (2005). The scout study: risk-benefit profile of sibutramine in overweight high-risk cardiovascular patients. *Eur. Heart J. Suppl*. 7, 44–48. doi:10.1093/eurheartj/sui086

Jena, B. S., Jayaprakasha, G. K., Singh, R. P., and Sakariah, K. K. (2002). Chemistry and biochemistry of (-)-hydroxycitric acid from Garcinia. *J. Agric. Food Chem*. 50, 10–22. doi:10.1021/jf010753k

Jeukendrup, A., and Randell, R. (2011). Fat burners: nutrition supplements that increase fat metabolism. *Obes. Rev.* 12, 841–851. doi:10.1111/j.1467-789X.2011.00908.x

Jull, A., Ni Mhurchu, C., Bennett, D., Dunshea-Mooij, C., and Rodgers, A. (2008). Chitosan for overweight or obesity. *Cochrane Database Syst. Rev.* 16, CD003892. doi:10.1002/14651858.CD003892.pub3

Keithley, J., and Swanson, B. (2005). Glucomannan and obesity: a critical review. *Alternative Ther. Health Med.* 11, 30–4.

Kelly, T., Yang, W., Chen, C. S., Reynolds, K., and He, J. (2008). Global burden of obesity in 2005 and projections to 2030. *Int. J. Obes.* 32, 1431–1437. doi:10.1038/ijo.2008.102

Kernan, W. N., Viscoli, C. M., Brass, L. M., Broderick, J. P., Brott, T., Feldmann, E., et al. (2000). Phenylpropanolamine and the risk of hemorrhagic stroke. *N. Engl. J. Med.* 343, 1826–1832. doi:10.1056/NEJM200012213432501

Kornacker, M., and Lowenstein, J. (1965). Citrate and the conversion of carbohydrate into fat. The activities of citrate-cleavage enzyme and acetate thiokinase in livers of starved and Re-fed rats. *Biochem. J.* 94, 209–215. doi:10.1042/bj0940209

Lean, M. E. (1997). Sibutramine--a review of clinical efficacy. *Int. J. Obes. Relat. Metab. Disord.* 21 (1), S30–S39.

Lejeune, M. P., Kovacs, E. M., and Westerterp-Plantenga, M. S. (2003). Effect of capsaicin on substrate oxidation and weight maintenance after modest body-weight loss in human subjects. *Br. J. Nutr.* 90, 651–659. doi:10.1079/bjn2003938

Lemus-Mondaca, R., Vega-Gálvez, A., Zura-Bravo, L., and Ah-Hen, K. (2012). Stevia rebaudiana Bertoni, source of a high-potency natural sweetener: a comprehensive review on the biochemical, nutritional and functional aspects. *Food Chem.* 132, 1121–1132. doi:10.1016/j.foodchem.2011.11.140

Li, Z., Maglione, M., Tu, W., Mojica, W., Arterburn, D., Shugarman, L. R., et al. (2005). Meta-analysis: pharmacologic treatment of obesity. *Ann. Intern. Med.* 142, 532–546. doi:10.7326/0003-4819-142-7-200504050-00012

Linn, T. C., and Srere, P. A. (1979). Identification of ATP citrate lyase as a phosphoprotein. *J. Biol. Chem.* 254, 1691–1698.

LiverTox (2012a). Clinical and research information on drug-induced liver injury Bethesda (MD): National institute of diabetes and digestive and kidney diseases. Garcinia cambogia. Available at: https://www.ncbi.nlm.nih.gov/books/NBK548087/ (Accessed February 13, 2019).

LiverTox (2012b). Clinical and research information on drug-induced liver injury Bethesda (MD): National institute of diabetes and digestive and kidney diseases. Lorcaserin. Available at: https://www.ncbi.nlm.nih.gov/books/NBK547852/ (Accessed May 6, 2020).

Lonneman, D. J., Rey, J. A., and McKee, B. D. (2013). Phentermine/Topiramate extended-release capsules (qsymia) for weight loss. *P T.* 38, 446–452.

Ludy, M. J., Moore, G. E., and Mattes, R. D. (2012). The effects of capsaicin and capsiate on energy balance: critical review and meta-analyses of studies in humans. *Chem. Senses.* 37, 103–121. doi:10.1093/chemse/bjr100

MacLean, D. B., and Luo, L. G. (2004). Increased ATP content/production in the hypothalamus may be a signal for energy-sensing of satiety: studies of the anorectic mechanism of a plant steroidal glycoside. *Brain Res.* 1020, 1–11. doi:10.1016/j.brainres.2004.04.041

Marso, S. P., Daniels, G. H., Brown-Frandsen, K., Kristensen, P., Mann, J. F., Nauck, M. A., et al. (2016). Liraglutide and cardiovascular outcomes in type 2 diabetes. *N. Engl. J. Med.* 375, 311–322. doi:10.1056/NEJMoa1603827

McCarty, M. F., and Majeed, M. (1994). "The pharmacology of citrin," in *Citrin: a ReVolutionary herbal approach to weight management*. Editor M. Majeed (Burlingame, CA: New Editions Publishing), 34–51.

McFee, R. B., Caraccio, T. R., McGuigan, M. A., Reynolds, S. A., and Bellanger, P. (2004). Dying to be thin: a dinitrophenol related fatality. *Vet. Hum. Toxicol.* 46, 251–254.

McNeely, W., and Goa, K. L. (1998). Sibutramine. a review of its contribution to the management of obesity. *Drugs.* 56, 1093–1124. doi:10.2165/00003495-199856060-00019

Mehta, A., Marso, S. P., and Neeland, I. J. (2017). Liraglutide for weight management: a critical review of the evidence. *Obes. Sci. Pract.* 3, 3–14. doi:10.1002/osp4.84

Mesa Ospina, N., Ospina Alvarez, S. P., Escobar Sierra, D. M., Rojas Vahos, D. F., Zapata Ocampo, P. A., and Ossa Orozco, C. P. (2015). Isolation of chitosan from Ganoderma lucidum mushroom for biomedical applications. *J. Mater. Sci. Mater. Med.* 26, 135. doi:10.1007/s10856-015-5461-z

Momtazi-Borojeni, A. A., Esmaeili, S. A., Abdollahi, E., and Sahebkar, A. (2017). A review on the pharmacology and toxicology of steviol glycosides extracted from Stevia rebaudiana. *Curr. Pharmaceut. Des.* 23, 1616–1622. doi:10.2174/1381612822666161021142835

Montan, P. D., Sourlas, A., Olivero, J., Silverio, D., Guzman, E., and Kosmas, C. E. (2019). Pharmacologic therapy of obesity: mechanisms of action and cardiometabolic effects. *Ann. Transl. Med.* 7, 393. doi:10.21037/atm.2019.07.27

Moraru, C., Mincea, M. M., Frandes, M., Timar, B., and Ostafe, V. (2018). A meta-analysis on randomised controlled clinical trials evaluating the effect of the dietary supplement chitosan on weight loss, lipid parameters and blood pressure. *Med.* 54, 1–15. doi:10.3390/MEDICINA54060109

Morris, M. J. (2018). Overview practice essentials. *Emedicine. Medscape.*, 1–35.

Musial, C., Kuban-Jankowska, A., and Gorska-Ponikowska, M. (2020). Beneficial properties of green tea catechins. *Int. J. Mol. Sci.* 21, 1744. doi:10.3390/ijms21051744

Narayanaswami, V., and Dwoskin, L. P. (2017). Obesity: current and potential pharmacotherapeutics and targets. *Pharmacol. Ther.* 170, 116–147. doi:10.1016/j.pharmthera.2016.10.015

National Institutes of Health Office of Dietary Supplements (2017). Available at: https://ods.od.nih.gov/factsheets/Carnitine-HealthProfessional/ (Accessed July 13, 2020).

Oketch-Rabah, H. A., Roe, A. L., Rider, C. V., Bonkovsky, H. L., Giancaspro, G. I., Navarro, V., et al. (2020). United States Pharmacopeia (USP) comprehensive review of the hepatotoxicity of green tea extracts. *Toxicol Rep.* 7, 386–402. doi:10.1016/j.toxrep.2020.02.008

Onakpoya, I., Hung, S. K., Perry, R., Wider, B., and Ernst, E. (2011a). The use of *Garcinia* extract (hydroxycitric acid) as a weight loss supplement: a systematic review and meta-analysis of randomised clinical trials. *J. Obes.* 2011, 509038. doi:10.1155/2011/509038

Onakpoya, I., Terry, R., and Ernst, E. (2011b). The use of green coffee extract as a weight loss supplement: a systematic review and meta-analysis of randomised clinical trials. *Gastroenterol Res Pract.*, 2011, 382852. doi:10.1155/2011/382852

Patanè, S., Marte, F., La Rosa, F. C., and La Rocca, R. (2010). Capsaicin and arterial hypertensive crisis. *Int. J. Cardiol.* 144, e26–e27. doi:10.1016/j.ijcard.2008.12.080

Pawar, R. S., Grundel, E., Fardin-Kia, A. R., and Rader, J. I. (2014). Determination of selected biogenic amines in Acacia rigidula plant materials and dietary supplements using LC-MS/MS methods. *J. Pharmaceut. Biomed. Anal.* 88, 457–466. doi:10.1016/j.jpba.2013.09.012

Pittler, M. H., and Ernst, E. (2001). Guar gum for body weight reduction: meta-analysis of randomized trials. *Am. J. Med.* 110, 724–730. doi:10.1016/s0002-9343(01)00702-1

Poddar, K., Kolge, S., Bezman, L., Mullin, G. E., and Cheskin, L. J. (2011). Nutraceutical supplements for weight loss: a systematic review. *Nutr. Clin. Pract.* 26, 539–552. doi:10.1177/0884533611419859

Pokhis, K., Bitterlich, N., Cornelli, U., and Cassano, G. (2015). Efficacy of polyglucosamine for weight loss-confirmed in a randomized double-blind, placebo-controlled clinical investigation. *BMC Obes.* 2, 25–28. doi:10.1186/s40608-015-0053-5

Pooyandjoo, M., Nouhi, M., Shab-Bidar, S., Djafarian, K., and Olyaeemanesh, A. (2016). The effect of (L-)carnitine on weight loss in adults: a systematic review and meta-analysis of randomized controlled trials. *Obes. Rev.* 17, 970–976. doi:10.1111/obr.12436

Porter, R. H., Benwell, K. R., Lamb, H., Malcolm, C. S., Allen, N. H., Revell, D. F., et al. (1999). Functional characterization of agonists at recombinant human 5-HT2A, 5-HT2B and 5-HT2C receptors in CHO-K1 cells. *Br. J. Pharmacol.* 128, 13–20. doi:10.1038/sj.bjp.0702751

Rapid Alert System for Food and Feed (RASFF) (2020). Available at: https://ec.europa.eu/food/safety/rasff/how_does_rasff_work/legal_basis (Accessed October 13, 2020).

Ríos-Hoyo, A., and Gutiérrez-Salmeán, G. (2016). New dietary supplements for obesity: what we currently know. *Curr. Obes. Rep.* 5, 262–270. doi:10.1007/s13679-016-0214-y

Rinaldi-Carmona, M., Barth, F., Héaulme, M., Alonso, R., Shire, D., Congy, C., et al. (1995). Biochemical and pharmacological characterisatioN OF SR141716A, the first potent and selective brain cannabinoid receptor antagonist. *Life Sci.* 56, 1941–1947. doi:10.1016/0024-3205(95)00174-5

Roza, O., Lovász, N., Zupkó, I., Hohmann, J., and Csupor, D. (2013). Sympathomimetic activity of a *Hoodia gordonii* product: a possible mechanism of cardiovascular side effects. *BioMed Res. Int.* 2013, 171059. doi:10.1155/2013/171059

Saito, M. (2015). Capsaicin and related food ingredients reducing body fat through the activation of TRP and Brown fat thermogenesis. *Adv. Food Nutr. Res.* 76, 1–28. doi:10.1016/bs.afnr.2015.07.002

Sam, A. H., Salem, V., and Ghatei, M. A. (2011). Rimonabant: from RIO to ban. *J. Obes.* 2011, 432607. doi:10.1155/2011/432607

Samenuk, D., Link, M. S., Homoud, M. K., Contreras, R., Theoharides, T. C., Wang, P. J., et al. (2002). Adverse cardiovascular events temporally associated with ma huang, an herbal source of ephedrine. *Mayo Clin. Proc.* 77, 12–16. doi:10.4065/77.1.12

Samuel, P., Ayoob, K. T., Magnuson, B. A., Wölwer-Rieck, U., Jeppesen, P. B., Rogers, P. J., et al. (2018). Stevia leaf to Stevia sweetener: exploring its science, benefits, and future potential. *J. Nutr.* 148, 1186S–1205S. doi:10.1093/jn/nxy102

Sanlier, N., Atik, A., and Atik, I. (2019). Consumption of green coffee and the risk of chronic diseases. *Crit. Rev. Food Sci. Nutr.* 59, 2573–2585. doi:10.1080/10408398.2018.1461061

Scheen, A. J., and Van Gaal, L. F. (2014). Combating the dual burden: therapeutic targeting of common pathways in obesity and type 2 diabetes. *Lancet Diabetes Endocrinol.* 2, 911–922. doi:10.1016/S2213-8587(14)70004-X

Schmid, A., Collomb, M., Sieber, R., and Bee, G. (2006). Conjugated linoleic acid in meat and meat products: a review. *Meat Sci.* 73, 29–41. doi:10.1016/j.meatsci.2005.10.010

Schteingart, D. E. (1992). Effectiveness of phenylpropanolamine in the management of moderate obesity. *Int. J. Obes. Relat. Metab. Disord.* 16, 487–493.

Sharma, A. M., Caterson, I. D., Coutinho, W., Finer, N., Van Gaal, L., Maggioni, A. P., et al. (2009). Blood pressure changes associated with sibutramine and weight management-an analysis from the 6-week lead-in period of the sibutramine cardiovascular outcomes trial (SCOUT). *Diabetes Obes. Metabol.* 11, 239–250. doi:10.1111/j.1463-1326.2008.00930.x

Sherman, M. M., Ungureanu, S., and Rey, J. A. (2016). Naltrexone/bupropion ER (contrave): newly approved treatment option for chronic weight management in obese adults. *P T.* 41, 164–172.

Shimoda, H., Seki, E., and Aitani, M. (2006). Inhibitory effect of green coffee bean extract on fat accumulation and body weight gain in mice. *BMC Compl. Alternative Med.* 6, 9. doi:10.1186/1472-6882-6-9

Shin, J. H., and Gadde, K. M. (2013). Clinical utility of phentermine/topiramate (Qsymia™) combination for the treatment of obesity. *Diabetes Metab Syndr Obes.* 6, 131–139. doi:10.2147/DMSO.S43403

Smith, S. R., Weissman, N. J., Anderson, C. M., Sanchez, M., Chuang, E., Stubbe, S., et al. (2010). Multicenter, placebo-controlled trial of lorcaserin for weight management. *N. Engl. J. Med.* 363, 245–256. doi:10.1056/NEJMoa0909809

Sood, N., Baker, W. L., and Coleman, C. I. (2008). Effect of glucomannan on plasma lipid and glucose concentrations, body weight, and blood pressure: systematic review and meta-analysis. *Am. J. Clin. Nutr.* 88, 1167–1175. doi:10.1093/ajcn/88.4.1167

Sullivan, A. C., Hamilton, J. G., Miller, O. N., and Wheatley, V. R. (1972). Inhibition of lipogenesis in rat liver by (-)-hydroxycitrate. *Arch. Biochem. Biophys.* 150, 183–190. doi:10.1016/0003-9861(72)90025-2

Tainter, M. L., Stockton, A. B., and Cutting, W. C. (1933). Use of Dinitrophenol in obesity and related conditions: a progress report. *J. Am. Med. Assoc.* 101, 1472–1475. doi:10.1001/jama.1933.02740440032009

Tainter, M. L., Cutting, W. C., and Stockton, A. B. (1934). Use of dinitrophenol in nutritional disorders : a critical survey of clinical results. *Am. J. Public Health Nation's Health.* 24, 1045–1053. doi:10.2105/ajph.24.10.1045

Tainter, M. L., Cutting, W. C., and Hines, E. (1935). Effects of moderate doses of dininitrophenol on the energy exchange and nitrogen metabolism of patients under conditions of restricted dietary. *J. Pharmacol. Exp. Therapeut.* 55, 326–353.

Tek, C. (2016). Naltrexone HCI/bupropion HCI for chronic weight management in obese adults: patient selection and perspectives. *Patient Prefer. Adherence.* 10, 751–759. doi:10.2147/PPA.S84778

The Plant List (2013). The plant list version 1.1. Available at: http://www.theplantlist.org/ (Accessed December 10, 2020).

The State Institute for Drug Control (SUKL) (2020). Czech republic Available at: http://www.sukl.eu/ (Accessed July 10, 2020).

Tonstad, S., Rössner, S., Rissanen, A., and Astrup, A. (2016). Medical management of obesity in Scandinavia 2016. *Obes. Med.* 1, 38–44. doi:10.1016/j.obmed.2016.01.002

van Heerden, F. R. (2008). Hoodia gordonii: a natural appetite suppressant. *J. Ethnopharmacol.* 119, 434–437. doi:10.1016/j.jep.2008.08.023

Vorsanger, M. H., Subramanyam, P., Weintraub, H. S., Lamm, S. H., Underberg, J. A., Gianos, E., et al. (2016). Cardiovascular effects of the new weight loss agents. *J. Am. Coll. Cardiol.* 68, 849–859. doi:10.1016/j.jacc.2016.06.007

Wadden, T. A., Berkowitz, R. I., Silvestry, F., Vogt, R. A., St. John Sutton, M. G., Stunkard, A. J., et al. (1998). The Fen-Phen finale: a study of weight loss and valvular heart disease. *Obes. Res.* 6, 278–284. doi:10.1002/j.1550-8528.1998.tb00350.x

Waibel, K. H., Haney, B., Moore, M., Whisman, B., and Gomez, R. (2011). Safety of chitosan bandages in shellfish allergic patients. *Mil. Med.* 176, 1153–1156. doi:10.7205/MILMED-D-11-00150

Walker, R. B., Fitz, L. D., Williams, L. M., and McDaniel, Y. M. (1996). The effect on ephedrine prodrugs on locomotor activity in rats. *Gen. Pharmacol.* 27, 109–111. doi:10.1016/0306-3623(95)00127-1

Watson, J. A., Fang, M., and Lowenstein, J. M. (1969). Tricarballylate and hydroxycitrate: substrate and inhibitor of ATP: citrate oxaloacetate lyase. *Arch. Biochem. Biophys.* 135, 209–217. doi:10.1016/0003-9861(69)90532-3

Weintraub, M., Sundaresan, P. R., Madan, M., Schuster, B., Balder, A., Lasagna, L., et al. (1992). Long-term weight control study. I (weeks 0 to 34). The enhancement of behavior modification, caloric restriction, and exercise by fenfluramine plus phentermine versus placebo. *Clin. Pharmacol. Ther.* 51, 586–594. doi:10.1038/clpt.1992.69

Wellam, P. J., and Sellers, T. L. (1986). Weight loss induced by chronic phenylpropanolamine: anorexia and brown adipose tissue thermogenesis. *Pharmacol. Biochem. Behav.* 24, 605–611. doi:10.1016/0091-3057(86)90565-4

Westerterp-plantenga, M. S., Lejeune, M. P. G. M., and Kovacs, E. M. R. (2005). Body weight loss and weight maintenance in relation to habitual caffeine intake and green tea supplementation. *Obes. Res.* 13, 1195–1204. doi:10.1038/oby.2005.142

Wharton, S., Bonder, R., Jeffery, A., and Christensen, R. A. G. (2020). The safety and effectiveness of commonly-marketed natural supplements for weight loss in populations with obesity: a critical review of the literature from 2006 to 2016. *Crit. Rev. Food Sci. Nutr.* 60, 1614–1630. doi:10.1080/10408398.2019.1584873

Whigham, L. D., O'Shea, M., Mohede, I. C., Walaski, H. P., and Atkinson, R. L. (2004). Safety profile of conjugated linoleic acid in a 12-month trial in obese humans. *Food Chem. Toxicol.* 42, 1701–1709. doi:10.1016/j.fct.2004.06.008

Whigham, L. D., Watras, A. C., and Schoeller, D. A. (2007). Efficacy of conjugated linoleic acid for reducing fat mass: a meta-analysis in humans. *Am. J. Clin. Nutr.* 85, 1203–1211. doi:10.1093/ajcn/85.5.1203

Whiting, S., Derbyshire, E. J., and Tiwari, B. (2014). Could capsaicinoids help to support weight management? A systematic review and meta-analysis of energy intake data. *Appetite.* 73, 183–188. doi:10.1016/j.appet.2013.11.005

Williams, G. (2010). Withdrawal of sibutramine in Europe. *BMJ.* 340, c824. doi:10.1136/bmj.c824

World Health Organization (2018). *Obesity and overweight*. Geneva, Switzerland: World Health Organization.

World Health Organization (2019). *Data and statistics- the challenge of obesity*. Geneva, Switzerland: World Health Organization.

Xiao, C., Gao, S., and Zhang, L. (2000). Blend films from konjac glucomannan and sodium alginate solutions and their preservative effect. *J. Appl. Polym. Sci.* 77, 617–626. doi:10.1002/(SICI)1097-4628(20000718)77:3<617::AID-APP17>3.0.CO;2-1

Yoshioka, M., St-Pierre, S., Suzuki, M., and Tremblay, A. (1998). Effects of red pepper added to high-fat and high-carbohydrate meals on energy metabolism

and substrate utilization in Japanese women. *Br. J. Nutr*. 80, 503–510. doi:10.1017/s0007114598001597

Yumuk, V., Tsigos, C., Fried, M., Schindler, K., Busetto, L., Micic, D., et al. (2015). European guidelines for obesity management in adults. *Obes. Facts*. 8, 402–424. doi:10.1159/000442721

Zalewski, B. M., and Szajewska, H. (2015). Effect of glucomannan supplementation on body weight in overweight and obese children: protocol of a randomised controlled trial. *BMJ Open*. 5, e007244–e007247. doi:10.1136/bmjopen-2014-007244

Zheng, J., Zheng, S., Feng, Q., Zhang, Q., and Xiao, X. (2017). Dietary capsaicin and its anti-obesity potency: from mechanism to clinical implications. *Biosci. Rep*. 37, BSR20170286. doi:10.1042/BSR20170286

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

nutrients

MDPI

Article

The Safety and Efficacy of *Citrus aurantium* (Bitter Orange) Extracts and *p*-Synephrine: A Systematic Review and Meta-Analysis

Dorottya Koncz [1], Barbara Tóth [1,2], Muh. Akbar Bahar [1,3], Orsolya Roza [4] and Dezső Csupor [1,2,4,*]

[1] Institute of Pharmacognosy, University of Szeged, 6720 Szeged, Hungary
[2] Institute for Translational Medicine, Medical School, University of Pécs, 7624 Pécs, Hungary
[3] Department of Pharmacy, Faculty of Pharmacy, Universitas Hasanuddin, Makassar 90245, Indonesia
[4] Institute of Clinical Pharmacy, University of Szeged, 6725 Szeged, Hungary
* Correspondence: csupor.dezso@szte.hu

Abstract: Synephrine has been used to promote weight loss; however, its safety and efficacy have not been fully established. The goals of our study were to give an overview of the safety and efficacy of *p*-synephrine, to systematically evaluate its efficacy regarding weight loss and to assess its safety, focusing on its cardiovascular side effects in a meta-analysis. PubMed, the Cochrane Library, Web of Science and Embase were searched for relevant studies. Only placebo-controlled, human clinical trials with synephrine intervention were included in the meta-analysis. The meta-analysis was reported according to the PRISMA guidelines using the PICOS format and taking into account the CONSORT recommendations. Altogether, 18 articles were included in the meta-analysis. Both systolic and diastolic blood pressure (DBP) increased significantly after prolonged use (6.37 mmHg, 95% CI: 1.02–11.72, $p = 0.02$ and 4.33 mmHg, 95% CI: 0.48–8.18, $p = 0.03$, respectively). The weight loss in the synephrine group was non-significant after prolonged treatment, and it did not influence body composition parameters. Based on the analyzed clinical studies, synephrine tends to raise blood pressure and heart rate, and there is no evidence that synephrine can facilitate weight loss. Further studies are needed to confirm evidence of its safety and efficacy.

Keywords: *p*-synephrine; meta-analysis; obesity; food supplements; weight loss

Citation: Koncz, D.; Tóth, B.; Bahar, M.A.; Roza, O.; Csupor, D. The Safety and Efficacy of *Citrus aurantium* (Bitter Orange) Extracts and *p*-Synephrine: A Systematic Review and Meta-Analysis. *Nutrients* **2022**, *14*, 4019. https://doi.org/10.3390/nu14194019

Academic Editor: Dalia El Khoury

Received: 10 September 2022
Accepted: 23 September 2022
Published: 28 September 2022

1. Introduction

The global increase in obesity is strongly connected to modifiable lifestyle factors, including sedentary lifestyle and diet [1]. Obesity is associated with serious health problems and related comorbidities [2,3], and even modest weight loss can result in improved systolic and diastolic blood pressure and blood cholesterol levels [4]. Increased physical activity, a low-calorie diet and the monitoring of body weight can facilitate weight loss in the long term [5].

Dietary supplements are easily available alternatives to medicines; however, data supporting their efficacy are usually scarce, and in some cases, their safety is also questionable [6]. Because of safety concerns, several Active Pharmaceutical Ingredients (APIs), that were considered as effective compounds to support weight loss are no longer available on the market. *p*-Synephrine, a protoalkaloid extracted from the immature fruit or peel of bitter orange (*Citrus* × *aurantium* L.), is widely used in weight loss and sports performance products [7], yet its efficacy and safety has not been fully established [8].

Synephrine exists in three different positional isomeric forms (ortho, meta and para) [9] (Figure 1). It is generally accepted that only *para*-synephrine (*p*-synephrine) can be found in bitter orange fruits [10–12]. Food supplements can contain *meta* (*m*)- and *p*-synephrine, which are both alpha-adrenergic agonists (α-agonists), while the *m*-isoform is the most potent on alpha-1-adrenoreceptors (α_1-adrenergic receptors) [13]. *Ortho*-synephrine

(*o*-synephrine) is not used as a pharmaceutical substance, and its natural occurrence has not been documented [13,14]. Methyl-synephrine HCl (4-HMP, *syn*. oxilofrine HCl) is a prohibited synthetic derivative of *p*-synephrine and has been reported as an adulterant in food supplements [15–18].

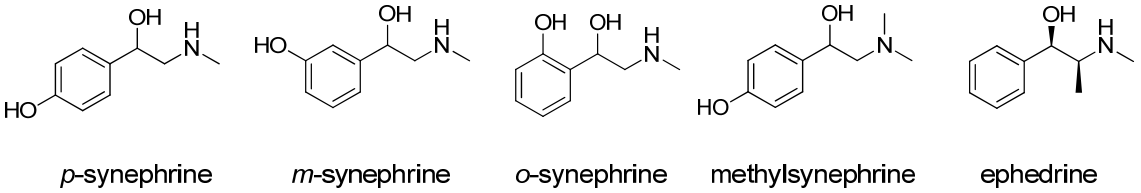


Figure 1. Structures of *para*-, *meta*- and *ortho*-synephrine, methyl-synephrine and ephedrine.

Since the use of ephedrine in food supplements has become prohibited in several European countries and in the USA, *p*-synephrine has gained considerable interest as the main substitute of ephedrine in weight loss products [12,19–21]. Synephrine is similar to ephedrine with regard to its structure and mechanism of action; however, it is less lipophilic, resulting in decreased transport through the blood–brain barrier [7,22–24]. The use of ephedrine is associated with the increased risk of myocardial infarction, hypertension, and stroke [12,25], but such pronounced effects on the cardiovascular system are not expected when using *p*-synephrine. Animal studies have shown that *p*-synephrine stimulates beta-adrenoreceptors, causing thermogenesis and lipolysis [7], whereas its cardiovascular adverse effects are partly due to its α-adrenergic receptor affinity [26]. Although it is generally acknowledged that *p*-synephrine has milder side effects than ephedrine, its safety and efficacy have not yet been thoroughly studied [8,19].

p-Synephrine (hereinafter referred to as synephrine) is used in pre-workout supplements to improve performance and to promote weight loss since it has thermogenic and sympathomimetic properties [27,28]. Synephrine was added to the Monitoring Program in Competitions of the World Anti-Doping Agency [29], but it is not yet considered as a prohibited substance (WADA) in 2022 [30]. However, it is prohibited for use by several professional sporting agencies (the National Collegiate Athletic Association (NCAA), Major League Baseball (MLB), and the National Football League (NFL)) [31].

Currently, there is little if any basis for making definitive statements about the safety of bitter orange extracts or synephrine used in food supplements [9]. Cardiac adverse events, including hypertension, tachyarrhythmia, variant angina, cardiac arrest, QT prolongation, ventricular fibrillation, myocardial infarction, and sudden death, have been the most common adverse effects associated with synephrine intake [27]; however, the prevalence is not known. The average synephrine content of the dried fruit extracts of *Citrus aurantium* has been reported to be between 3% and 6% [9,10,32–34]. The French food safety authority (ANSES) concluded in its assessment on synephrine [35] that the intake levels of synephrine from food supplements must remain below 20 mg/day, and it is not recommended to take synephrine in combination with caffeine. It is also recommended to avoid the use of products containing synephrine during physical exercise, and its use by sensitive individuals is discouraged (i.e., people taking certain medications, pregnant or breastfeeding women, children, and adolescents) [35,36]. Because of its known sympathomimetic properties and adrenergic effects on the cardiovascular system, the use of synephrine in food supplements is debated [36]. Even though there is no legislation which limits the content of synephrine and other alkaloids in dietary supplements, based on the Directive 2002/46/EC, each country is supposed to set a maximum level of synephrine [37,38]. There have been reports in the RASFF (Rapid Alert System for Food and Feed) about synephrine, because in some countries, there is a limit regarding its daily dose, and in the reported cases, the products contained more than the maximum [39] (Table S1, Figure S1).

2. Materials and Methods

2.1. Literature Search and Selection Criteria

Electronic searches were conducted in the following databases: PubMed, Embase, Web of Science (WoS), and the Cochrane Library. Each database was searched until 17 August 2022. The searching method included the key term synephrine. This meta-analysis of eligible peer reviewed studies was reported in accordance with the PRISMA statement and followed the CONSORT recommendations. Trials were selected if they were (1) human clinical studies, (2) compared known doses of orally used synephrine with a placebo or active control or both, and (3) completed. In order to complete this task, the following PICO (patients, intervention, comparison, outcome) format was applied: P: adults; I: known dosage of *p*-synephrine given per os; C: placebo or control; and O: changes in the body weight, composition, cardiovascular, and metabolic parameters (i.e., heart rate, blood pressure, body weight, body fat, fat mass, fat-free mass, fasting blood sugar level, and RER values). Our hypothesis was that synephrine facilitates weight loss and that its use correlated with cardiovascular adverse effects. This work was registered in PROSPERO (359626). There were no restrictions regarding the number of included patients or the minimal or maximal dosing of *p*-synephrine. The language of the included articles was restricted to English.

2.2. Data Extraction and Endpoints

As clarified in the PICO, clinical trials involving adults were included in this meta-analysis. Of these clinical trials, outcomes related to the efficacy and safety of synephrine were extracted. The study endpoints included those values which were present in at least three articles and could be compared. Statistical evaluation could modify the finally analyzed trials/outcomes. The following information from individual studies was extracted: the first author's name and publication year; the study design and population; the number of participants; other medicines in the intervention group; synephrine regimen; and outcomes.

2.3. Quality Evaluations

Two authors (D.K. and D.CS.) performed the literature search. Both authors reviewed the full-text articles and extracted appropriate data from the publications. The risk of bias was analyzed by two of the authors (D.CS. and B.T.), using the Cochrane Risk of Bias Tool, which includes the following domains: random sequence generation, allocation concealment, the blinding of participants and personnel, the blinding of outcome assessment, incomplete outcome data, selective reporting and other scores of bias. For each domain, studies were judged to have a high (red), unclear (yellow), or low (green) risk of bias (Figure S2 and S3). Disagreements were resolved by consensus. Risk of bias figures were prepared by using the Review Manager (RevMan) version 5.4.1 software from Cochrane Training site based in London, UK.

2.4. Statistical Analysis

An outcome was selected for the final analysis if it was reported in at least three articles; however, further attrition and unique time intervals could modify the analyzed study number/outcome. The assessment of weighted mean difference (MD) and effect sizes (ESs) between test and control group values (synephrine vs. control) was performed as a post–post analysis. A Chi^2 or Tau^2 test was used to evaluate the heterogeneity. Deviating study intervention arms were excluded from the final analysis in case there were other extra intervention(s) apart from synephrine (mainly caffeine). In the case of heterogenous subjects based on their caffeine usage, the regular non-caffeine users were selected contrasting to regular high caffeine users. The statistical analyses were conducted using the Review Manager 5.4.1 software. The results were considered statistically significant when the p value was less than 0.05.

3. Results

3.1. Literature Search

The literature search resulted in the identification of 2435 articles (Figure 2). After duplicate removal, the screening of 1472 titles and abstracts resulted in the revision of 51 publications which were retrieved for full-text screening (excluded: n = 1421). The 51 full-text articles were assessed for eligibility. After the revision, 21 studies were found to be appropriate for qualitative analysis (excluded: n = 30). Articles were excluded if they were not peer reviewed scientific articles (i.e., abstracts or posters) (n = 2); were clinical trials but not with synephrine (n = 3); were not human clinical studies (n = 1); when there were time intervals that were too heterogeneous or did not indicate trial duration (n = 5). Further studies were excluded if they had missing statistical values (n = 1) or detailed outcomes (n = 7), or missing relevant outcomes (n = 4), they were not placebo-controlled trials (n = 3) or were not clinical studies (n = 4). Since one study [40] was open-label and in two studies, the authors did not give the exact dosage of synephrine [41,42], these studies were not eligible for further quantitative analyses. Therefore, a total of 18 studies involving 341 patients were included in the final quantitative analysis. Penzak et al. conducted a two-way, crossover, open-label trial and assessed the cardiovascular effect of approx. 13–14 mg synephrine, which did not significantly alter SBP, DBP, and HR in 12 healthy subjects [40]. Kliszczewicz et al. reported a randomized crossover trial investigating the effects of 100 mg of *Citrus aurantium* (CA) powder (with an unknown dosage of synephrine) compared to caffeine (100 mg) or a placebo. The consumption of *Citrus aurantium* caused a significant time-dependent increase in the HR of the test subjects [41]. In another randomized, double-blind trial, participants consumed 140 mL of a high-energy drink containing unknown dosages of methyl-synephrine [42]. Based on their results, significantly higher SBP was observed in the intervention group during the three-hour study period, but no significant changes were observed in HR or in DBP.

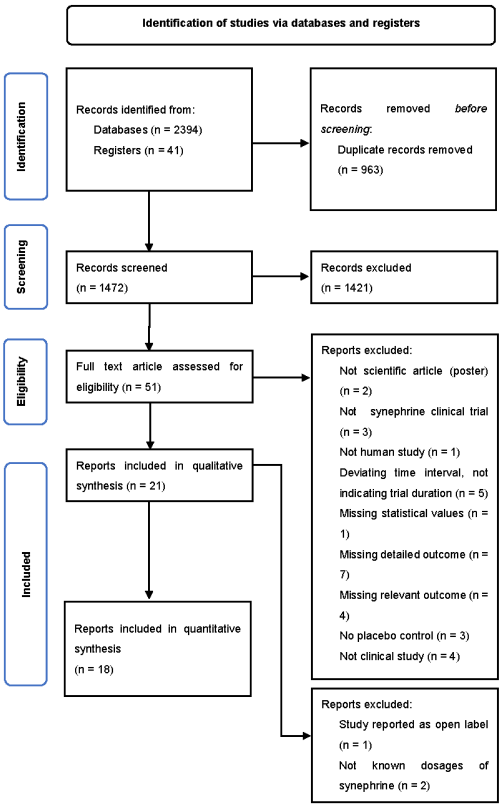


Figure 2. A flow diagram for identification of relevant studies.

3.1.1. Characteristics of the Trials

The 18 trials included were double-blinded, prospective, parallel or crossover, within-subjects or counterbalanced studies (Table S2). Seven trials were crossover [43–49]; five had parallel design [22,50–53]; four had within-subjects [54,55] or other [56,57] designs; and two were performed in a counterbalanced manner [58,59].

Fourteen trials assessed the acute effects of synephrine [43–49,53–59]. In four trials, the effect of a longer treatment duration (a range of 4–8 weeks) was assessed [22,50–52]. The daily dosage of synephrine ranged from 6 to 214 mg.

The inclusion criteria of the trials varied from trial to trial. Eight trials only included physically active subjects [22,45,49,50,52,54,56,59]. In eight trials, healthy, normotensive but not resistance-trained subjects were involved [43,44,46,48,51,53,55,57]. Four trials included overweight adults [22,47,52,58]. In several trials, other interventions were also studied, but these study arms were not included in our analysis [45,50,51,53–56]. Nine trials involved exercise training [22,45,49,50,52,56–59]. It is important to emphasize that while comparing weight loss and body compositions from the analyzed three articles [22,50,52], all of these trials included exercise intervention, and two involved dietary restrictions [22,52]. Nine trials did not include exercise intervention [43,44,46–48,51,53–55]. In seven trials, the main analyzed intervention contained substances other than synephrine (e.g., caffeine) [22,44,45,47,50,52,58]. One study [56] claimed that all participants were classified as low caffeine consumers (<50 mg/day), but in the rest of the trials, the authors did not specify whether the subjects were regular or non-regular caffeine users. Bush et al. (2018) [54] and Ratamess et al. (2018) [55] divided groups based on their average caffein consumption. However, the subgroup of regular high caffeine users (>300 mg) was excluded from our final meta-analysis to make the analyzed groups more homogenous. In seven trials, participants were requested to limit caffeine consumption [22,49,51,52,56,57,59].

3.1.2. Demography of the Patients

In the 18 trials analyzed, the common inclusion criterion was the age of 18 years or older, and in every study, the inclusion procedure was in harmony with the Helsinki declaration. In eight cases, pregnant women were excluded [22,43–46,48,51,52], and also, smoking was an exclusion criterion; only non-smokers participated in nine trials [43,45,49,50,54–56,58,59]. The age of the analyzed participants was between 18 and 51 years. Participants were healthy, physically active/exercise trained or in fewer cases, healthy but sedentary and/or overweight. Additionally, more male patients were randomized (68.45%). Taking into consideration the crossover design and the within subject design, 341 subjects were analyzed (Table S3).

3.2. Outcomes

The meta-analyzed outcomes were SBP, DBP, HR, weight loss, body fat percentage, fat mass, fat-free mass, blood glucose, and RER values. In addition, several studies indicated other adverse events, but they were too heterogeneous to be statistically analyzed. These side effects included complaints of headaches [46], hyperventilation [58], racing HR, feelings of dizziness, and feelings of irritability or perspiration [55], palpitations, shortness of breath, nervousness, and blurred vision [50]. Other outcomes were increased VO_2 uptake [45], increased energy expenditure [44], increased fat oxidation, reduced carbohydrate utilization [57,59], and changes in the ratings of perceived exertion [56,59]. However, the outcomes mentioned above were omitted from the final analysis, since these occurred in less than three articles or were based on other heterogeneous parameters (time intervals) or missing detailed outcomes.

3.2.1. Cardiovascular Parameters

Altogether, 11 trials with 222 subjects and six different time sets and heterogeneous dosages (a range of 10–214 mg) were used to assess the effects of synephrine on blood pressure. The SBP tended to increase in the synephrine group (Figure 3). It was found

that 30–45 min after the administration of 20–50 mg of synephrine, the mean difference was 1.21 mmHg (95% CI: −2.57–5.00), which was not significant ($p = 0.53$) but showed a greater effect size for synephrine than for the placebo. After 1 h of the administration of the products containing 49–214 mg of synephrine, the post–post analysis showed a non-significant increase in the SBP (MD 1.56 mmHg, 95% CI: −1.11–4.24, $p = 0.25$). Based on five trials involving 61 subjects, the effect of synephrine (49–180 mg) remained non-significant (MD 3.89 mmHg, 95% CI: −0.99–8.77, $p = 0.12$) after 2 h. After 3 h of the administration, only a slight effect (MD 0.34 mmHg, 95% CI: −2.18–2.87, $p = 0.79$) on the SBP was observable, and it seems that the effect diminished after 6-8 h (MD 0.10 mmHg, 95% CI: −3.82–4.02, $p = 0.96$; dosage 27–108 mg) of consumption. Based on two trials involving 75 subjects, a daily dose of 10–49 mg of synephrine had a significant effect on the systolic blood pressure (MD 6.37 mmHg, 95% CI: 1.02–11.72, $p = 0.02$) after 8 weeks of administration.

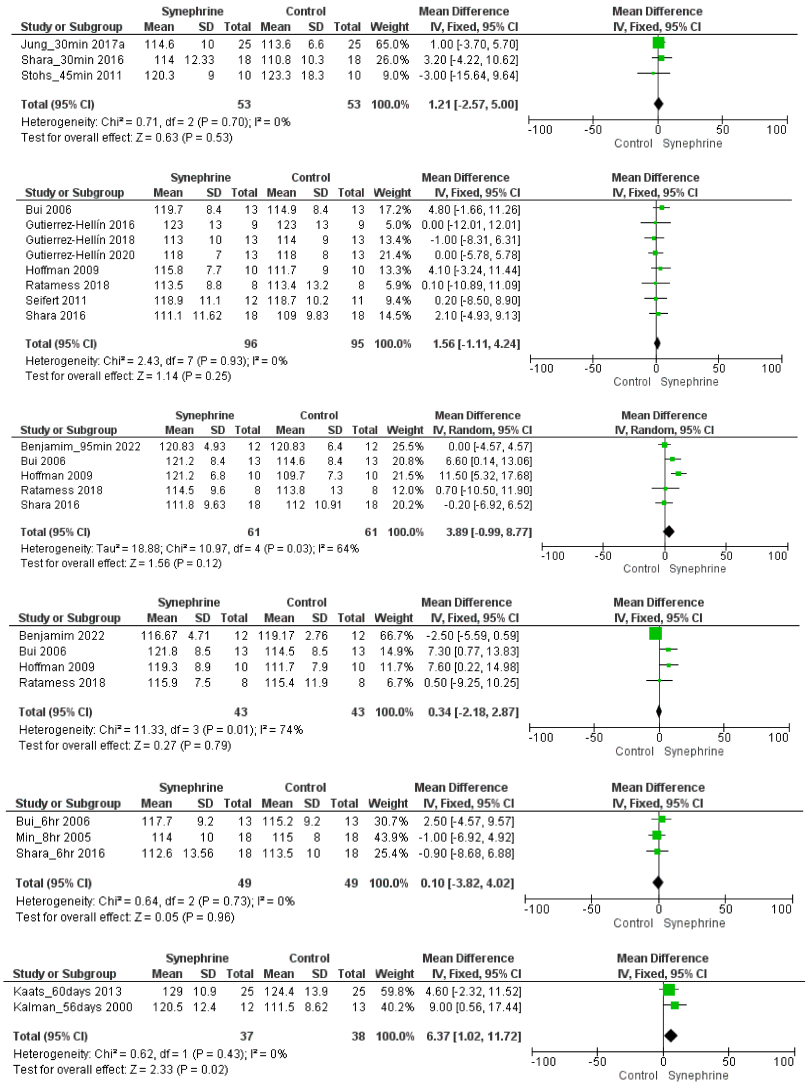


Figure 3. Forest plot diagram of synephrine on systolic blood pressure acutely (after 30–45 min; 1 h; 2 h; 3 h; and 6–8 h) and long-duration (56–60 days) in intervention and control groups.

The dosages and the included articles were the same in DBP; one difference was that we left one datum point out by 2 h [49], as the statistical SD value "0" could not have been estimated. The administration of synephrine (20–214 mg) did not significantly alter the DBP 30-45 min after administration (MD: −0.88 mmHg, 95% CI: −4.45–2.70, $p = 0.63$); 1 h after administration (MD: −0.89 mmHg, 95% CI: −2.92–1.13, $p = 0.39$); 2 h after administration (MD: 0.48 mmHg 95% CI: −2.22–3.17, $p = 0.73$) (four articles; 49 subjects; 49–108 mg);

3 h after administration (MD: 0.40 mmHg 95% CI: −1.83–2.62, $p = 0.73$); or 6-8 h after administration (MD: −0.43 mmHg 95% CI: −3.52–2.66, $p = 0.78$).

Based on two trials involving 75 participants, a significant effect was observed on DBP after the long-term (8 weeks) usage of 10–49 mg of synephrine (MD 4.33 mmHg, 95% CI: 0.48–8.18, $p = 0.03$) (Figure 4).

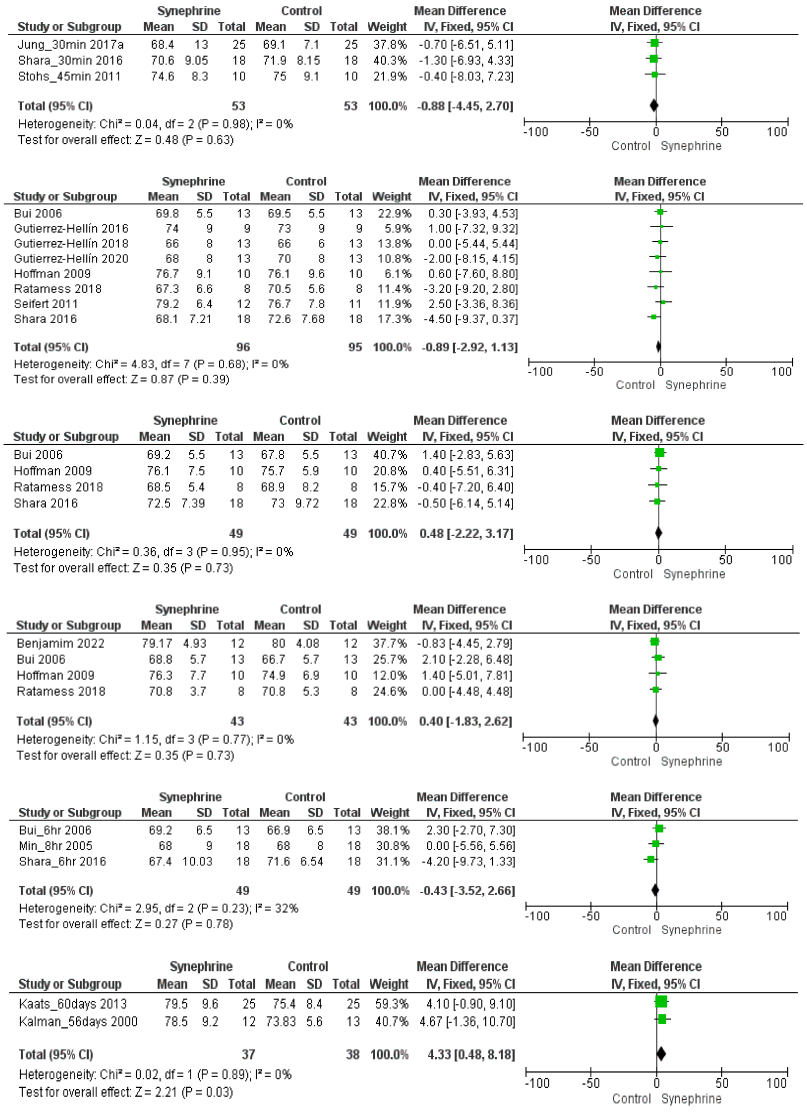


Figure 4. Forest plot diagram of synephrine on diastolic blood pressure acutely (after 30–45 min; 1 h; 2 h; 3 h; and 6–8 h) and long duration (56–60 days) in intervention and control groups.

Overall, nine trials involving 129 persons with six different time durations and varying dosages of synephrine (range 20–214 mg) studied the effects of synephrine on heart rate. Significant differences between synephrine and the placebo were not reported; however, the heart rate slightly increased after 30 min–6 h from consumption in the synephrine group (Figure 5). It was found that 30–45 min after synephrine consumption (20–50 mg), the mean difference in heart rate was 3.15 beat/min (95% CI: −0.41–6.71, $p = 0.08$); and it was 1.11 beat/min (95% CI: −1.32–3.53, $p = 0.37$) 1 h after the consumption of varying doses (49–214 mg) of synephrine. After 2 h of the ingestion of 49–180 mg of synephrine, a non-significant rise in the heart rate was observed (MD 3.15 beat/min, 95% CI: −0.65–6.96, $p = 0.10$).

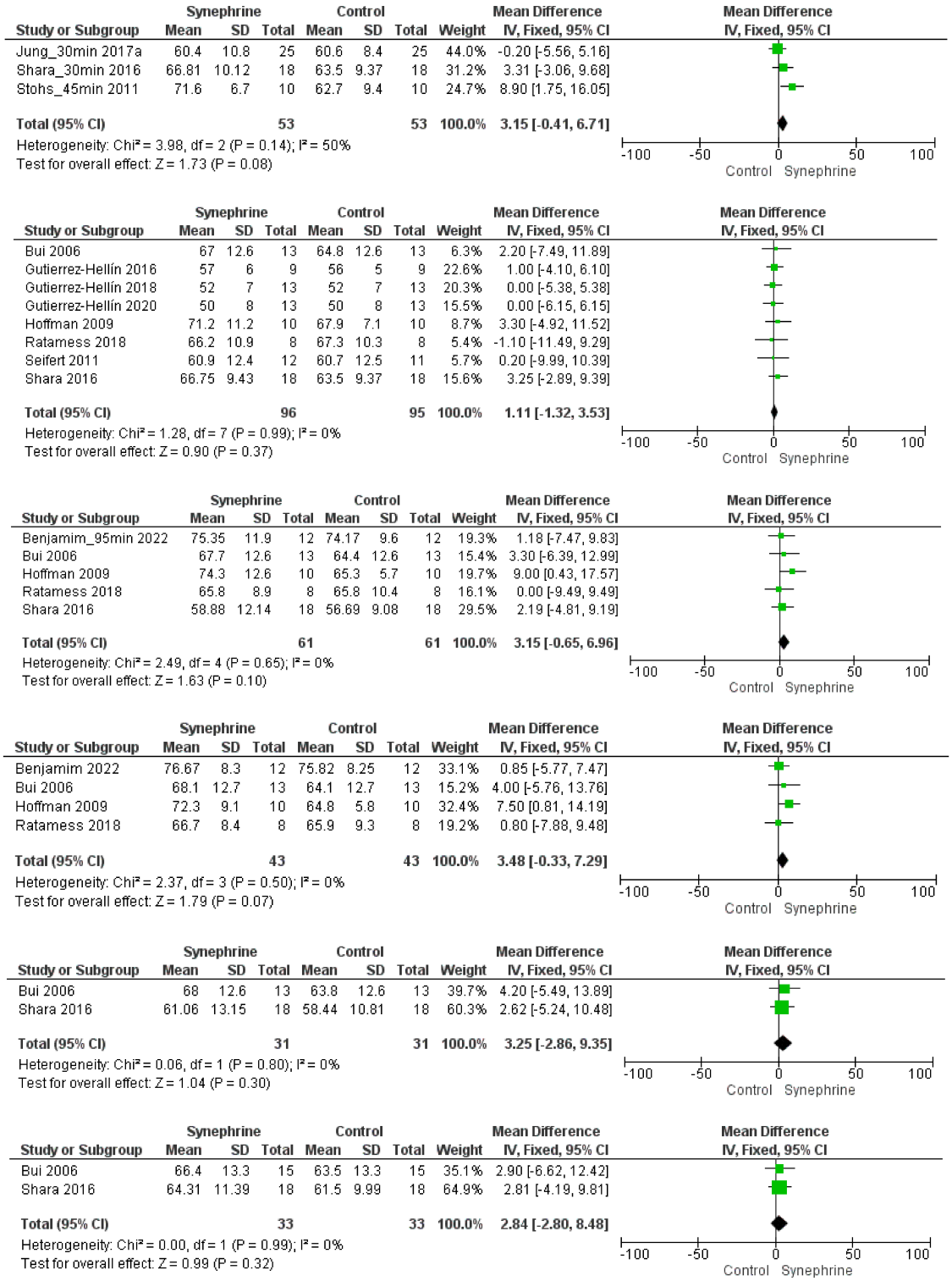


Figure 5. Forest plot diagram of synephrine on heart rate acutely (after 30–45 min; 1 h; 2 h; 3 h; 4 h; and 6 h) in intervention and control groups.

Based on four trials involving 43 subjects, 3 h after the consumption of 60–180 mg of synephrine, the synephrine-adjusted increase in heart rate was 3.48 beat/min (95% CI: −0.33–7.29, $p = 0.07$). The effects observed after 4 h (MD 3.25 beat/min, 95% CI: −2.86–9.35,

p = 0.30) and after 6 h (MD 2.84 beat/min, 95% CI: −2.80–8.48, p = 0.32; range 49–108 mg) remained non-significant based on the articles involving these time points.

3.2.2. Weight Loss and Body Composition

The effect of synephrine on weight loss was analyzed in three trials [22,50,52]. The trials lasted for several weeks (42–56 days or 6–8 weeks), and the daily dose of synephrine was 54 mg, 20 mg, and 10 (5 × 2) mg, respectively. Based on our meta-analysis, its effect on weight loss was non-significant (MD 0.60 kg, 95% CI: −5.62–6.83, p = 0.85) (Figure 6A). The consumption of synephrine only resulted in a slight decrease in body fat (−1.87%, 95% CI; −3.92–0.18, p = 0.07), and the effect was not statistically different from that of the placebo (Figure 6B).

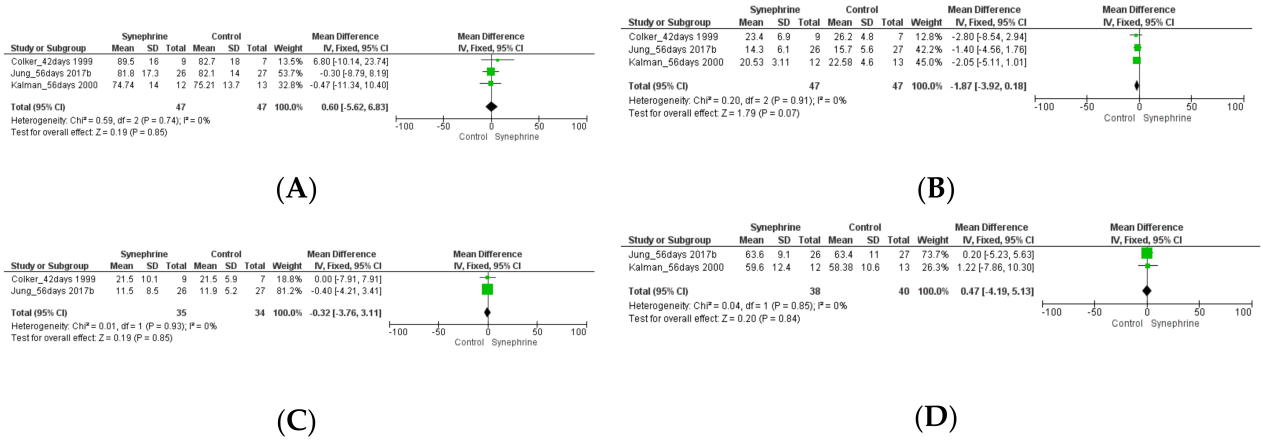


Figure 6. Forest plot diagram of synephrine on weight and body composition from (6–8 weeks) 42–56 days in intervention and control groups: (**A**) weight, (**B**) body fat, (**C**) fat mass, and (**D**) fat-free mass.

The administration of synephrine (20 or 54 mg) did not result in significant changes in fat mass. The mean difference was −0.32 kg (95% CI: −3.76–3.11, p = 0.85) (Figure 6C). A low dosage of synephrine (10 and 20 mg) did not significantly change the fat-free mass based on the included trials (MD 0.47 kg, 95% CI: −4.19–5.13, p = 0.84) (Figure 6D).

3.2.3. Other Outcomes

Based on the included trials, blood glucose values were not changed significantly after the administration of 6–103 mg of synephrine. Blood glucose levels changed slightly but not significantly after 2–3 h of the consumption of synephrine (MD 4.62 mg/dL, 95% CI: −3.04–12.29, p = 0.24) with moderate heterogeneity (TAU^2 = 30.32%) (Figures 7 and S4). In the head-to-head studies, the effect of synephrine on blood and plasma glucose [45,54,58] was also not significant.

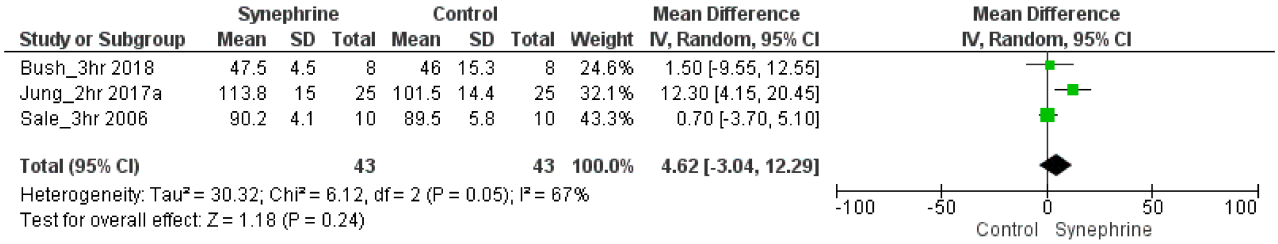


Figure 7. Forest plot diagram of synephrine acutely on blood glucose in intervention and control groups.

The acute effects of synephrine (6–60 mg) on the respiratory exchange ratio (RER) were studied in three trials [44,47,58]. The effect of synephrine was not significant after 1, nor after 2, nor after 3 h of administration. After 1 h of consumption, there was no difference (the mean difference was 0.00 (95% CI: −0.03–0.03, p = 0.91)), strengthened by a

non-classical leave-one-out analysis. After 2 h, synephrine resulted in a −0.02 difference (95% CI: −0.12–0.09, $p = 0.75$), and after 3 h, synephrine resulted in a −0.02 difference (95% CI: −0.12–0.08, $p = 0.73$) (Figure S5).

3.3. Risk of Bias

Overall, the methodical quality of the trials included in our final quantitative analysis was reckoned to be acceptable, mostly with low or unclear risks of bias (Figures S2 and S3).

The random sequence generation was described in three studies [43,48,49], and the measures taken to ensure allocation concealment were given in eight trials [43,45,49,50,54,55,57,59]; therefore, the selection bias (i.e., random sequence generation or allocation concealment) in these studies was judged to be low. On the other hand, Sale et al. [58] failed to mention whether their study was randomized or not; therefore, it had a high risk of selection bias. In the remaining studies, the information to judge the selection bias was not available; therefore, these studies were reckoned to have unclear risks of selection bias.

Regarding to the performance bias, four studies [43,49,50,59] were judged to have low risks of bias, but in the case of 14 studies, it was not clear whether the treatment and the comparator were identical in size, shape, color, and odor, and who was blinded and until when was not clearly described; therefore, these studies were judged to have unclear risks of performance bias. Four studies had low risks of detection bias [43,46,56,57], but in the other 14 studies, it remained unclear whether the results were assessed in a blinded manner or not.

All the included studies showed low risks of attrition and reporting biases. Five studies had unclear risks of bias, since all of these studies were at least partly founded by pharmaceutical companies related to the studied products, but their influence on the study design, performance, and report are not clearly stated [48,53–55,58].

4. Discussion

Overall, 18 trials involving 341 adults were analyzed to perform this meta-analysis. Different sets depending on each outcome were applied to assess the weight loss effects of synephrine and to establish its safety based on its effects on cardiovascular variables. Based on the literature, the commonly used doses of *p*-synephrine vary from 25 to 100 mg per day [16,60,61], while our analysis included 6–214 mg of synephrine. Based on our meta-analysis, synephrine did not significantly increase systolic blood pressure acutely, but it significantly increased in the long term ($p = 0.02$) (Figure 3). It had less significant acute effects on diastolic blood pressure and showed similarly significant effects when applied for longer durations (8 weeks) ($p = 0.03$) (Figure 4). After the acute administration of synephrine, the heart rate increased, but the change remained non-significant; the highest increase was measured 3 h after consumption ($p = 0.07$) (Figure 5). Our analysis led to the conclusion that the prolonged use of synephrine did not result in significant alterations in body weight and composition (Figure 6). Based on the analyzed data, the acute administration of synephrine did not change blood glucose and RER values (Figures 7 and S5).

Synephrine's impacts on cardiovascular health can be predicted by looking at its effects on cardiovascular variables. Since the use of ephedrine is associated with the increased risk of cardiovascular morbidity and mortality, a similarly effective but safe alternative would be greatly appreciated [9,62]. The dosage used during weight loss analysis was 10–54 mg daily for 42–56 days, which nearly coincides with the dosage that resulted in cardiovascular adverse events (increased blood pressure) after 56–60 days after the administration of 10–49 mg of synephrine. Based on our results, the use of synephrine does not lack cardiovascular side effects; therefore, it may not be a safe alternative to ephedrine for those with predisposing comorbidities.

p-Synephrine-containing products are marketed for those aiming for higher energy utilization during low- to moderate-intensity exercise [8]. However, it is not yet proven that bitter orange or synephrine consumption can reduce body fat or promote weight loss [8].

Based on our meta-analysis, the prolonged use of synephrine does not result in significant weight loss ($p = 0.85$). A mean difference of 0.6 kg was observed in a total of 94 subjects (47 subjects/intervention with a daily dose of 10–54 mg of synephrine). Synephrine was ineffective in influencing body fat (−1.87%, $n = 94$, $p = 0.07$), fat mass (−0.32 kg, $n = 69$, $p = 0.85$), and fat-free mass (−0.47 kg, $n = 78$, $p = 0.84$).

Some results suggest that *p*-synephrine has the potential to maintain blood glucose levels by stimulating the uptake of excess blood glucose via insulin-dependent or -independent mechanisms in skeletal muscles [63]. Maintaining optimal blood glucose values would be beneficial, suggesting greater hepatic glucose release, which would be favorable during exercise [45,64]. Based on our results, consuming synephrine did not alter blood glucose levels significantly ($p = 0.24$), and blood glucose maintenance was not affected by the consumption of 6–103 mg of synephrine.

Higher RER values indicate that carbohydrates are being predominantly used as fuel, and lower RER values suggest lipid oxidation [65,66]. Physically active and trained subjects exhibit lower RER values than untrained sedentary subjects in response to comparable workloads [67–69]. Our analysis included three articles with 33 analyzed subjects overall. In these trials, the effects of synephrine were assessed after 1 h of consumption. After 2–3 h of consumption, data from only 20 subjects were available. Our results suggest that the consumption of 6-103 mg of synephrine does not modify RER values significantly. RER value changes in the studies were presumably related to caffeine, and all three of the analyzed trials administered a supplement which had additional caffeine in it [47].

The strengths of this systematic review with meta-analysis are that only data from published peer-reviewed articles were used, and all the included trials were double-blind trials. However, there are several limitations to the analysis. First, the studied products were different and contained varying doses (6–214 mg) of synephrine with different isometric forms. One study included both *m*- and *p*-synephrine [46], and one study examined the effects of methyl-synephrine HCl [44]. Only six studies included isolated *p*-synephrine [53–57,59]. In the remaining ten studies, the applied products (such as bitter orange extract) contained standardized synephrine [43,48,49] or were mixed with other substances [22,44,45,47,50,52,58]. The main limitation of the study was high attrition, and only a few studies assessed the same outcomes, resulting in relatively small plots. There were no mentions of the the subjects' ethnicities, which weakens the results, as it is not clear if the groups were diverse enough in this regard. On the other hand, subjects showed a high variety of traits regarding physical activity and age, and more males were analyzed. Some trials included an exercise intervention, which made the data more heterogonous. Previously, Stohs et al. performed a detailed systematic review of synephrine, but there was no meta-analysis on this topic with statistical evaluations; only a literature review was performed [70]. The only available meta-analysis examined oral phenylephrine on nasal airway resistance in patients with nasal congestion, which did not examine *p*-synephrine and did not analyze its weight loss effects [71].

5. Conclusions

After the ban of *Ephedra sinica* by the FDA in 2004, there was a clear need for an alternative weight loss supplement with favorable safety profile [12,25]. Synephrine was widely used to promote weight loss, and it is often considered as a safe and effective option, but its safety and efficacy is yet to be studied. When applying synephrine, it should be taken into account that it also has sympathomimetic effects, so it may also increase systolic blood pressure, diastolic blood pressure, and heart rate. Consequently, it may also increase the risk for stroke and myocardial infarction and therefore harm the consumers' health. Hence, the hemodynamic effects of bitter orange and *p*-synephrine must be established, but unfortunately, studies related to synephrine-induced cardiotoxicity are scarce [27,43].

p-Synephrine showed a tendency to increase systolic blood pressure and heart rate acutely, and it significantly increased both systolic and diastolic blood pressure when applied for longer durations. Therefore, our meta-analysis revealed safety concerns related

to the use of synephrine. The beneficial effects of synephrine were rather inconclusive. In our meta-analysis, it did not promote weight loss, and neither did it cause beneficial effects on body composition. The overall effects on glucose and RER values were not proved to be favorable. The currently available evidence indicates that synephrine influences blood pressure and heart rate but has no significant effects on weight loss and body composition; therefore, its use is not recommended to promote health. Considering the limitations, it is concluded that further and larger trials are needed to assess the efficacy and safety of synephrine with a lower risk of bias.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/nu14194019/s1, Table S1: Unauthorized synephrine (above maximal limit) products in the European Union in the RASFF system from 1988 to 2019; Table S2: Characteristics of the trials; Table S3: Demography of patients; Figure S1. Unauthorized synephrine (above maximal limit) products in the RASFF system from 2007 to 2019 (accessed on 31 December 2019).; Figure S2: Risk of bias graph on synephrine meta-analysis; Figure S3: Risk of bias summary on synephrine meta-analysis; Figure S4: Forest plot diagram of synephrine on (h/2) blood glucose for short duration in intervention and control groups with one change in the time duration; Figure S5: Forest plot diagram of synephrine on (i) *RER* values after 1–3 h (1 h two times with one change in time interval) in intervention and control groups.

Author Contributions: Conceptualization, D.K. and D.C.; methodology, D.C.; software, M.A.B. and B.T.; formal analysis, D.K.; investigation, D.K. and D.C.; data curation, B.T., D.C. and M.A.B.; writing—original draft preparation, D.K.; writing—review and editing, D.C., O.R. and B.T.; visualization, B.T., M.A.B. and D.K.; supervision, O.R. All authors have read and agreed to the published version of the manuscript.

Funding: Project No. TKP2021-EGA-32 has been implemented with the support provided by the Ministry of Innovation and Technology of Hungary from the National Research, Development and Innovation Fund, financed under the TKP2021-EGA funding scheme.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available in this article and in the Supplementary Material.

Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Abbreviations

ANSES	The French Agency for Food, Environmental and Occupational Health & Safety
BP	Blood pressure
CA	*Citrus aurantium*
CI	Confidence interval
DBP	Diastolic blood pressure
HCL	Hydrochloride
HR	Heart rate
E	Epinephrine
EC	European Commission
EE	Energy expenditure
EU	European Union
FDA	U.S. Food and Drug Administration
MD	Mean difference
NA	Noradrenaline
NE	Norepinephrine
NK	Not known
mmHg	Millimeters of mercury
m-synephrine	*Meta*-synephrine (phenylephrine)
p-synephrine	*Para*-synephrine
QT	Measurement made on electrocardiogram. It is calculated as the time from the start of the Q wave to the end of the T wave.
RASFF	Rapid Alert System for Food and Feed
RCT	Randomized clinical trial
RER	Respiratory exchange ratio
SBP	Systolic blood pressure
SD	Standard deviation
VO2	Oxygen consumption
4-HMP	Methyl-synephrine HCl, oxiflorine

References

1. Stoner, L.; Rowlands, D.; Morrison, A.; Credeur, D.; Hamlin, M.; Gaffney, K.; Lambrick, D.; Matheson, A. Efficacy of Exercise Intervention for Weight Loss in Overweight and Obese Adolescents: Meta-Analysis and Implications. *Sports Med.* **2016**, *46*, 1737–1751. [CrossRef] [PubMed]
2. Finucane, M.M.; Stevens, G.A.; Cowan, M.J.; Danaei, G.; Lin, J.K.; Paciorek, C.J.; Singh, G.M.; Gutierrez, H.R.; Lu, Y.; Bahalim, A.N.; et al. National, Regional, and Global Trends in Body-Mass Index since 1980: Systematic Analysis of Health Examination Surveys and Epidemiological Studies with 960 Country-Years and 9·1 Million Participants. *Lancet* **2011**, *377*, 557–567. [CrossRef]
3. Sarma, S.; Sockalingam, S.; Dash, S. Obesity as a Multisystem Disease: Trends in Obesity Rates and Obesity-Related Complications. *Diabetes Obes. Metab.* **2021**, *23*, 3–16. [CrossRef]
4. Ryan, D.H.; Yockey, S.R. Weight Loss and Improvement in Comorbidity: Differences at 5%, 10%, 15%, and Over. *Curr. Obes. Rep.* **2017**, *6*, 187–194. [CrossRef] [PubMed]
5. Wadden, T.A.; Tronieri, J.S.; Butryn, M.L. Lifestyle Modification Approaches for the Treatment of Obesity in Adults. *Am. Psychol.* **2020**, *75*, 235–251. [CrossRef] [PubMed]
6. Koncz, D.; Tóth, B.; Kiss, T.; Roza, O.; Csupor, D. Acacia Rigidula versus Other Acacia Taxa: An Alarming Issue in the European Novel Food Regulation and Food Supplement Industry. *Acta Pharm. Hung.* **2021**, *91*, 67–74. [CrossRef]
7. Stohs, S.J.; Preuss, H.G.; Shara, M. The Safety of *Citrus aurantium* (Bitter Orange) and Its Primary Protoalkaloid p-Synephrine. *Phyther. Res.* **2011**, *25*, 1421–1428. [CrossRef]
8. Ruiz-Moreno, C.; Del Coso, J.; Giráldez-Costas, V.; González-García, J.; Gutiérrez-Hellín, J. Effects of P-Synephrine during Exercise: A Brief Narrative Review. *Nutrients* **2021**, *13*, 233. [CrossRef] [PubMed]
9. Haaz, S.; Fontaine, K.R.; Cutter, G.; Limdi, N.; Perumean-Chaney, S.; Allison, D.B. *Citrus aurantium* and Synephrine Alkaloids in the Treatment of Overweight and Obesity: An Update. *Obes. Rev.* **2006**, *7*, 79–88. [CrossRef]
10. Andrade, A.S.; Schmitt, G.C.; Rossato, L.G.; Russowsky, D.; Limberger, R.P. Gas Chromatographic Method for Analysis of P-Synephrine in *Citrus aurantium* L. Products. *Chromatographia* **2009**, *69*, S225–S229. [CrossRef]
11. Arbo, M.D.; Larentis, E.R.; Linck, V.M.; Aboy, A.L.; Pimentel, A.L.; Henriques, A.T.; Dallegrave, E.; Garcia, S.C.; Leal, M.B.; Limberger, R.P. Concentrations of P-Synephrine in Fruits and Leaves of Citrus Species (Rutaceae) and the Acute Toxicity Testing of *Citrus aurantium* Extract and p-Synephrine. *Food Chem. Toxicol.* **2008**, *46*, 2770–2775. [CrossRef] [PubMed]
12. Fugh-Berman, A.; Myers, A. *Citrus aurantium*, an Ingredient of Dietary Supplements Marketed for Weight Loss: Current Status of Clinical and Basic Research. *Exp. Biol. Med.* **2004**, *229*, 698–704. [CrossRef] [PubMed]
13. Rossato, L.G.; de Pinho, P.G.; Silva, R.; Carmo, H.; Carvalho, F.; Bastos, M.D.L.; Costa, V.M.; Remião, F. Development and Validation of a GC/IT-MS Method for Simultaneous Quantitation of Para and Meta-Synephrine in Biological Samples. *J. Pharm. Biomed. Anal.* **2010**, *52*, 721–726. [CrossRef] [PubMed]
14. Santana, J.; Sharpless, K.E.; Nelson, B.C. Determination of Para-Synephrine and Meta-Synephrine Positional Isomers in Bitter Orange-Containing Dietary Supplements by LC/UV and LC/MS/MS. *Food Chem.* **2008**, *109*, 675–682. [CrossRef]
15. Pawar, R.S.; Grundel, E. Overview of Regulation of Dietary Supplements in the USA and Issues of Adulteration with Phenethylamines (PEAs). *Drug Test. Anal.* **2017**, *9*, 500–517. [CrossRef] [PubMed]
16. Stohs, S.J. Safety, Efficacy, and Mechanistic Studies Regarding *Citrus aurantium* (Bitter Orange) Extract and p-Synephrine. *Phyther. Res.* **2017**, *31*, 1463–1474. [CrossRef] [PubMed]
17. Vaysse, J.; Balayssac, S.; Gilard, V.; Desoubdzanne, D.; Malet-Martino, M.; Martino, R. Analysis of Adulterated Herbal Medicines and Dietary Supplements Marketed for Weight Loss by DOSY 1H-NMR. *Food Addit. Contam.—Part A Chem. Anal. Control Expo. Risk Assess.* **2010**, *27*, 903–916. [CrossRef] [PubMed]
18. Cohen, P.A.; Avula, B.; Venhuis, B.; Travis, J.C.; Wang, Y.-H.; Khan, I.A. Pharmaceutical Doses of the Banned Stimulant Oxilofrine Found in Dietary Supplements Sold in the USA. *Drug Test. Anal.* **2017**, *9*, 135–142. [CrossRef] [PubMed]
19. Thomas, J.E.; Munir, J.A.; McIntyre, P.Z.; Ferguson, M.A. STEMI in a 24-Year-Old Man after Use of a Synephrine-Containing Dietary Supplement: A Case Report and Review of the Literature. *Tex. Heart Inst. J.* **2009**, *36*, 586–590.
20. Palamar, J. How Ephedrine Escaped Regulation in the United States: A Historical Review of Misuse and Associated Policy. *Health Policy* **2011**, *99*, 1–9. [CrossRef]
21. EFSA. Scientific Opinion on Safety Evaluation of Ephedra Species for Use in Food. *EFSA J.* **2013**, *11*, 3467. [CrossRef]
22. Colker, C.M.; Kalman, D.S.; Torina, G.C.; Perlis, T.; Street, C. Effects of *Citrus aurantium* Extract, Caffeine, and St. John's Wort on Body Fat Loss, Lipid Levels, and Mood States in Overweight Healthy Adults. *Curr. Ther. Res. Exp.* **1999**, *60*, 145–153. [CrossRef]
23. Arch, J.R.S. B3-Adrenoceptor Agonists: Potential, Pitfalls and Progress. *Eur. J. Pharmacol.* **2002**, *440*, 99–107. [CrossRef]
24. Jones, D. Citrus and Ephedra. *Whole Foods* **2004**, *40*, 40–41.
25. Haller, C.A.; Benowitz, N.L. Adverse Cardiovascular and Central Nervous System Events Associated with Dietary Supplements Containing Ephedra Alkaloids. *N. Engl. J. Med.* **2000**, *343*, 1833–1838. [CrossRef]
26. Inchiosa, M.A. Experience (Mostly Negative) with the Use of Sympathomimetic Agents for Weight Loss. *J. Obes.* **2011**, *2011*, 764584. [CrossRef] [PubMed]
27. Rossato, L.G.; Costa, V.M.; Limberger, R.P.; de Lourdes Bastos, M.; Remião, F. Synephrine: From Trace Concentrations to Massive Consumption in Weight-Loss. *Food Chem. Toxicol.* **2011**, *49*, 1472–1473. [CrossRef]
28. Haller, C.A.; Duan, M.; Jacob III, P.; Benowitz, N. Human Pharmacology of a Performance-Enhancing Dietary Supplement under Resting and Exercise Conditions. *Br. J. Clin. Pharmacol.* **2008**, *65*, 833–840. [CrossRef] [PubMed]

29. Docherty, J.R. Pharmacology of Stimulants Prohibited by the World Anti-Doping Agency (WADA). *Br. J. Pharmacol.* **2008**, *154*, 606–622. [CrossRef] [PubMed]
30. WADA. The Prohibited List. Available online: https://www.wada-ama.org/en/prohibited-list (accessed on 20 August 2022).
31. Piattoly, T.J. Dietary Supplement Safety: Risk vs Reward for Athletes. *Oper. Tech. Sports Med.* **2022**, *30*, 150891. [CrossRef]
32. Arbo, M.D.; Schmitt, G.C.; Limberger, M.F.; Charão, M.F.; Moro, A.M.; Ribeiro, G.L.; Dallegrave, E.; Garcia, S.C.; Leal, M.B.; Limberger, R.P. Subchronic Toxicity of *Citrus aurantium* L. (Rutaceae) Extract and p-Synephrine in Mice. *Regul. Toxicol. Pharmacol.* **2009**, *54*, 114–117. [CrossRef] [PubMed]
33. Avula, B.; Upparapalli, S.K.; Navarrete, A.; Khan, I.A. Simultaneous Quantification of Adrenergic Amines and Flavonoids in C. Aurantium, Various Citrus Species, and Dietary Supplements by Liquid Chromatography. *J. AOAC Int.* **2005**, *88*, 1593–1606. [CrossRef] [PubMed]
34. Peixoto, J.S.; Comar, J.F.; Moreira, C.T.; Soares, A.A.; de Oliveira, A.L.; Bracht, A.; Peralta, R.M. Effects of *Citrus aurantium* (Bitter Orange) Fruit Extracts and p-Synephrine on Metabolic Fluxes in the Rat Liver. *Molecules* **2012**, *17*, 5854–5869. [CrossRef] [PubMed]
35. ANSES. Opinion of the French Agency for Food, Environmental and Occupational Health & Safety on the Risks Associated with the Presence in Food Supplements of P-synephrine or Ingredients Obtained from Citrus Spp. Fruits Containing This Substance. Available online: https://www.anses.fr/en/content/opinion-french-agency-food-environmental-and-occupational-health-safety-risks-associated-1 (accessed on 21 August 2022).
36. Bakhyia, N.; Dusemund, B.; Richter, K.; Lindtner, O.; Hirsch-Ernst, K.I.; Schäfer, B.; Lampen, A. Risk assessment of synephrine in dietary supplements. *Bundesgesundheitsblatt. Gesundheitsforschung. Gesundheitsschutz* **2017**, *60*, 323–331. [CrossRef]
37. European Parliament. Directive 2002/46/CE. *Off. J. Eur. Communities* **2002**, *45*, 51–57.
38. Haššo, M.; Sarakhman, O.; Stanković, D.M.; Švorc, Ľ. A New Voltammetric Platform for Reliable Determination of the Sport Performance-Enhancing Stimulant Synephrine in Dietary Supplements Using a Boron-Doped Diamond Electrode. *Anal. Methods* **2020**, *12*, 4749–4758. [CrossRef]
39. RASFF. Food and Feed Safety Alerts. Available online: https://ec.europa.eu/food/safety/rasff/how_does_rasff_work/legal_basis_en (accessed on 31 December 2019).
40. Penzak, S.R.; Jann, M.W.; Cold, J.A.; Hori, Y.Y.; Desai, H.D.; Gurley, B.J. Seville (Sour) Orange Juice: Synephrine Content and Cardiovascular Effects in Normotensive Adults. *J. Clin. Pharmacol.* **2001**, *41*, 1059–1063. [CrossRef]
41. Kliszczewicz, B.; Bechke, E.; Williamson, C.; Bailey, P.; Hoffstetter, W.; McLester, J.; McLester, C. The Influence of *Citrus aurantium* and Caffeine Complex versus Placebo on the Cardiac Autonomic Response: A Double Blind Crossover Design. *J. Int. Soc. Sports Nutr.* **2018**, *15*, 34. [CrossRef]
42. Rashti, S.L.; Ratamess, N.A.; Kang, J.; Faigenbaum, A.D.; Chilakos, A.; Hoffman, J.R. Thermogenic Effect of Meltdown RTD Energy Drink in Young Healthy Women: A Double Blind, Cross-over Design Study. *Lipids Health Dis.* **2009**, *8*, 57. [CrossRef]
43. Bui, L.T.; Nguyen, D.T.T.; Ambrose, P.J. Blood Pressure and Heart Rate Effects Following a Single Dose of Bitter Orange. *Ann. Pharmacother.* **2006**, *40*, 53–57. [CrossRef]
44. Hoffman, J.R.; Kang, J.; Ratamess, N.A.; Rashti, S.L.; Tranchina, C.P.; Faigenbaum, A.D. Thermogenic Effect of an Acute Ingestion of a Weight Loss Supplement. *J. Int. Soc. Sports Nutr.* **2009**, *6*, 1. [CrossRef] [PubMed]
45. Jung, Y.P.; Earnest, C.P.; Koozehchian, M.; Galvan, E.; Dalton, R.; Walker, D.; Rasmussen, C.; Murano, P.S.; Greenwood, M.; Kreider, R.B. Effects of Acute Ingestion of a Pre-Workout Dietary Supplement with and without p-Synephrine on Resting Energy Expenditure, Cognitive Function and Exercise Performance. *J. Int. Soc. Sports Nutr.* **2017**, *14*, 3. [CrossRef] [PubMed]
46. Min, B.; Cios, D.; Kluger, J.; White, C.M. Absence of QTc-Interval-Prolonging or Hemodynamic Effects of a Single Dose of Bitter-Orange Extract in Healthy Subjects. *Pharmacotherapy* **2005**, *25*, 1719–1724. [CrossRef]
47. Seifert, J.G.; Nelson, A.; Devonish, J.; Burke, E.R.; Stohs, S.J. Effect of Acute Administration of an Herbal Preparation on Blood Pressure and Heart Rate in Humans. *Int. J. Med. Sci.* **2011**, *8*, 192–197. [CrossRef]
48. Shara, M.; Stohs, S.J.; Mukattash, T.L. Cardiovascular Safety of Oral P-Synephrine (Bitter Orange) in Healthy Subjects: A Randomized Placebo-Controlled Cross-over Clinical Trial. *Phyther. Res.* **2016**, *30*, 842–847. [CrossRef]
49. Benjamim, C.J.R.; de Sousa Júnior, F.W.; Porto, A.A.; Rocha, É.M.B.; Santana, M.D.; Garner, D.M.; Valenti, V.E.; Bueno Júnior, C.R. Bitter Orange (*Citrus aurantium* L.) Intake Before Submaximal Aerobic Exercise Is Safe for Cardiovascular and Autonomic Systems in Healthy Males: A Randomized Trial. *Front. Nutr.* **2022**, *9*, 890388. [CrossRef] [PubMed]
50. Jung, Y.P.; Earnest, C.P.; Koozehchian, M.; Cho, M.; Barringer, N.; Walker, D.; Rasmussen, C.; Greenwood, M.; Murano, P.S.; Kreider, R.B. Effects of Ingesting a Pre-Workout Dietary Supplement with and without Synephrine for 8 Weeks on Training Adaptations in Resistance-Trained Males. *J. Int. Soc. Sports Nutr.* **2017**, *14*, 1. [CrossRef]
51. Kaats, G.R.; Miller, H.; Preuss, H.G.; Stohs, S.J. A 60day Double-Blind, Placebo-Controlled Safety Study Involving *Citrus aurantium* (Bitter Orange) Extract. *Food Chem. Toxicol.* **2013**, *55*, 358–362. [CrossRef]
52. Kalman, D.S.; Colker, C.M.; Shi, Q.; Swain, M.A. Effects of a Weight-Loss Aid in Healthy Overweight Adults: Double-Blind, Placebo-Controlled Clinical Trial. *Curr. Ther. Res.-Clin. Exp.* **2000**, *61*, 199–205. [CrossRef]
53. Stohs, S.J.; Preuss, H.G.; Keith, S.C.; Keith, P.L.; Miller, H.; Kaats, G.R. Effects of P-Synephrine Alone and in Combination with Selected Bioflavo-Noids on Resting Metabolism, Blood Pressure, Heart Rate and Self-Reported Mood Changes. *Int. J. Med. Sci.* **2011**, *8*, 295–301. [CrossRef]

54. Bush, J.A.; Ratamess, N.A.; Stohs, S.J.; Ellis, N.L.; Vought, I.T.; O'Grady, E.A.; Kuper, J.D.; Kang, J.; Faigenbaum, A.D. Acute Hematological and Mood Perception Effects of Bitter Orange Extract (p-Synephrine) Consumed Alone and in Combination with Caffeine: A Placebo-Controlled, Double-Blind Study. *Phyther. Res.* **2018**, *32*, 1593–1607. [CrossRef] [PubMed]
55. Ratamess, N.A.; Bush, J.A.; Stohs, S.J.; Ellis, N.L.; Vought, I.T.; O'Grady, E.A.; Kuper, J.D.; Hasan, S.B.; Kang, J.; Faigenbaum, A.D. Acute Cardiovascular Effects of Bitter Orange Extract (p-Synephrine) Consumed Alone and in Combination with Caffeine in Human Subjects: A Placebo-Controlled, Double-Blind Study. *Phyther. Res.* **2018**, *32*, 94–102. [CrossRef] [PubMed]
56. Gutierrez-Hellin, J.; Del Coso, J. Dose-Response Effects of p-Synephrine on Fat Oxidation Rate During Exercise of Increasing Intensity. *Phyther. Res.* **2018**, *32*, 370–374. [CrossRef] [PubMed]
57. Gutierrez-Hellin, J.; Ruiz-Moreno, C.; Del Coso, J. Acute P-Synephrine Ingestion Increases Whole-Body Fat Oxidation during 1-h of Cycling at Fatmax. *Eur. J. Nutr.* **2020**, *59*, 3341–3345. [CrossRef] [PubMed]
58. Sale, C.; Harris, R.C.; Delves, S.; Corbett, J. Metabolic and Physiological Effects of Ingesting Extracts of Bitter Orange, Green Tea and Guarana at Rest and during Treadmill Walking in Overweight Males. *Int. J. Obes.* **2006**, *30*, 764–773. [CrossRef] [PubMed]
59. Gutiérrez-Hellín, J.; Del Coso, J. Acute P-Synephrine Ingestion Increases Fat Oxidation Rate during Exercise. *Br. J. Clin. Pharmacol.* **2016**, *82*, 362–368. [CrossRef]
60. Stohs, S.J.; Shara, M.; Ray, S.D. P-Synephrine, Ephedrine, p-Octopamine and m-Synephrine: Comparative Mechanistic, Physiological and Pharmacological Properties. *Phytother. Res.* **2020**, *34*, 1838–1846. [CrossRef]
61. Suntar, I.; Khan, H.; Patel, S.; Celano, R.; Rastrelli, L. An Overview on *Citrus aurantium* L.: Its Functions as Food Ingredient and Therapeutic Agent. *Oxid. Med. Cell. Longev.* **2018**, *2018*, 7864269. [CrossRef]
62. Samenuk, D.; Link, M.S.; Homoud, M.K.; Contreras, R.; Theoharides, T.C.; Wang, P.J.; Estes, N.A.M., 3rd. Adverse Cardiovascular Events Temporally Associated with Ma Huang, an Herbal Source of Ephedrine. *Mayo Clin. Proc.* **2002**, *77*, 12–16. [CrossRef]
63. Park, D.; Lee, D.; Lee, Y. P-Synephrine Stimulates Glucose Consumption via AMPK in L6 Skeletal Muscle Cells. *Diabetes* **2012**, *61*, A469–A470. [CrossRef]
64. Kratz, A.; Lewandrowski, K.B.; Siegel, A.J.; Chun, K.Y.; Flood, J.G.; Van Cott, E.M.; Lee-Lewandrowski, E. Effect of Marathon Running on Hematologic and Biochemical Laboratory Parameters, Including Cardiac Markers. *Am. J. Clin. Pathol.* **2002**, *118*, 856–863. [CrossRef] [PubMed]
65. Simonson, D.C.; DeFronzo, R.A. Indirect Calorimetry: Methodological and Interpretative Problems. *Am. J. Physiol. Metab.* **1990**, *258*, E399–E412. [CrossRef] [PubMed]
66. Pendergast, D.R.; Leddy, J.J.; Venkatraman, J.T. A Perspective on Fat Intake in Athletes. *J. Am. Coll. Nutr.* **2000**, *19*, 345–350. [CrossRef]
67. Jeukendrup, A.E.; Mensink, M.; Saris, W.H.M.; Wagenmakers, A.J.M. Exogenous Glucose Oxidation during Exercise in Endurance-Trained and Untrained Subjects. *J. Appl. Physiol.* **1997**, *82*, 835–840. [CrossRef]
68. Bergman, B.C.; Brooks, G.A. Respiratory Gas-Exchange Ratios during Graded Exercise in Fed and Fasted Trained and Untrained Men. *J. Appl. Physiol.* **1999**, *86*, 479–487. [CrossRef] [PubMed]
69. Ramos-Jiménez, A.; Hernández-Torres, R.P.; Torres-Durán, P.V.; Romero-Gonzalez, J.; Mascher, D.; Posadas-Romero, C.; Juárez-Oropeza, M.A. The Respiratory Exchange Ratio Is Associated with Fitness Indicators Both in Trained and Untrained Men: A Possible Application for People with Reduced Exercise Tolerance. *Clin. Med. Circ. Respir. Pulm. Med.* **2008**, *2*, CCRPM.S449. [CrossRef]
70. Stohs, S.J.; Preuss, H.G.; Shara, M. A Review of the Human Clinical Studies Involving *Citrus aurantium* (Bitter Orange) Extract and Its Primary Protoalkaloid p-Synephrine. *Int. J. Med. Sci.* **2012**, *9*, 527–538. [CrossRef]
71. Hatton, R.C.; Winterstein, A.G.; McKelvey, R.P.; Shuster, J.; Hendeles, L. Efficacy and Safety of Oral Phenylephrine: Systematic Review and Meta-Analysis. *Ann. Pharmacother.* **2007**, *41*, 381–390. [CrossRef]