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Effect on Weight Loss of an Oral Supplement Containing Cinnamon Bark (*Cinnamomum cassia*) and *Withania somnifera* in Adult Patients with Overweight and Obesity: A Pilot Study

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Abstract: With the prevalence of obesity soaring and the absence of an effective and safe treatment that is low-cost and always feasible, food supplements have gained attention for their potential benefits in the absence of significant safety concerns. *Cinnamomum cassia* (CC) and *Withania somnifera* (WS) are plant-based supplements reported to be effective in improving metabolic health and body composition, the first mainly acting on insulin resistance and the second on energy expenditure and leptin resistance, as shown in preclinical and some clinical studies. Their combination, which is possibly synergistic given their different mechanisms of action, has never been studied. This was a double-blind placebo-controlled study. Patients with overweight or obesity were prescribed a mildly hypocaloric diet with 300 mg CC plus 150 mg WS tid for 4 weeks in a crossover design; anthropometric parameters and safety outcomes were collected. Forty patients were enrolled, and the combination CC + WS induced significant weight loss compared with placebo (−2.66% vs. −1.28%, respectively; $p = 0.0002$). No significant adverse events were recorded. Our study demonstrates for the first time that the tested combination is an inexpensive yet effective strategy to enhance weight loss in patients receiving a mildly hypocaloric diet. Further studies are warranted to investigate the mechanisms underlying the weight loss effect of CC/WS in human subjects, as well as to explore potential additional metabolic effects obtained with this treatment.

Keywords: food supplements; botanicals; metabolic syndrome; nutraceuticals; phytotherapy

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1. Introduction

The prevalence of overweight and obesity is rapidly increasing all over the world [1–3]. The clinical and social relevance of obesity relates to its contributory role in the development of chronic diseases, including cancer [4], diabetes [5], and liver [6] and cardiovascular diseases [7]. Other emerging complications of excess weight are gaining attention and will likely add to the burden in the future [8]. Although genetic traits play an etiological role in the majority of the leading global causes of death [9], it appears that unhealthy lifestyles and social factors prevail over genetic predisposition as the main causes of the increased mortality risk for patients with obesity [10].

Effective strategies to prevent and treat obesity are scarce. As a consequence, a rise in body mass index (BMI) and body weight in the US population between 1999 and 2016 occurred, despite the proportion of those attempting to lose weight increasing from 34.3% to 42.2% in the same period [1]. Among the most commonly reported strategies

for losing weight, reduced food intake, increased exercise, and frequent water intake are those with the most rapidly increasing prevalence [1]. Specific dietary interventions, such as the dietary approaches to stop hypertension (DASH) [11], the ORNISH [12], or the ketogenic diet (Atkins, Dukan, protein-sparing modified fast, etc.,) find their role in aiding weight loss and treating obesity-related complications [13]; however, although they are generally safe, they may not be applicable to everybody [14] and long-term compliance represents a challenge. Even the Mediterranean diet, despite possibly being the optimum to prevent obesity, has been questioned regarding its efficacy for inducing significant weight loss and maintenance [15]. Anti-obesity pharmacologic strategies have been developed, with some promising results. Lorcaserin is a selective serotonin 2C receptor agonist that modulates appetite and has been shown to significantly increase weight loss through a central mechanism of appetite reduction [16,17]. Despite its statistical significance, the clinical relevance of the obtained weight reduction has been questioned and safety concerns have emerged [18,19]. Agonists of the key mediator of anorexia and reduced food intake, i.e., the GLP-1 receptor, as well as the combination of buproprion/naltrexone, are safe and effective; however, their use is limited by the cost, which is required to be met by the patient in most countries [20–22]. Moreover, pharmacotherapy is usually only indicated when the patient's BMI is over 27 and at least one obesity complication is present, leaving those who are mildly overweight and yet to develop complications with only lifestyle interventions as possible treatments. An inexpensive, widely applicable, and safe strategy to increase long-term compliance to lifestyle changes, and particularly to healthy eating patterns, is therefore much needed.

The use of dietary supplements to support weight loss and metabolic improvement in patients with overweight or obesity is frequent, and some have proven to be beneficial in small studies [23–26]; however, current evidence on their efficacy is controversial [27–29]. The lack of convincing pre-clinical data and the poor design of clinical trials, together with an unstandardized method of manufacturing and delivering the active compounds, may explain the failure of translating preliminary evidence into effective strategies. In this regard, only nutrients with a demonstrated mechanism of action should be considered for clinical testing.

Cinnamon is a spice that has been used all over the world for a long time. It is derived from the inner bark of trees belonging to the genus *Cinnamomum*, Lauraceae family, of which *C. cassia* (CC) is one of the most widespread and used. The active compounds range from cinnamaldehyde, cinnamic acid, coumarin, and eugenol, with antibacterial properties [30], to glutathione and polyphenols that exert antioxidant properties [31], together with an insulin-sensitizing and secretagogue effect [32,33]. Interestingly, it has been shown that cinnamon regulates the expression of genes involved in both lipid and carbohydrate metabolism in murine models [34], as well as inducing the browning of subcutaneous adipose tissue and therefore increasing energy expenditure and improving weight loss in obese mice and rats [35,36]. A recent systematic review showed that cinnamon supplementation was able to induce a minimal yet significant body weight loss (−1.02 kg, 95% CI: −1.66 to −0.38, $p = 0.002$), especially when the diet duration was over 12 weeks, when patients were young and their BMI was $\geq$30 kg/m^2 [37]. Of note, dosages of $\geq$2 g/d were found to be the most effective. Despite being generally considered safe, cinnamon may lead to adverse events in a dose-dependent manner, and such aspects should be kept in consideration when increasing the daily dosage [38,39].

Withania somnifera (i.e., ashwagandha in Ayurvedic medicine) (WS) is a plant in the Solanaceae family; its roots are traditionally used to promote strength. Its active compounds are alkaloids, steroidal lactones, tannin, and flavonoids. The administration of WS has been proven to induce anti-inflammatory, anti-oxidant and anti-cancer effects [40]. It was recently shown that WS extract restores sensitivity to leptin in an animal model of obesity via the action of its main component, withaferin A [41], and that it increases energy expenditure through mitochondrial function improvement in fat and skeletal muscle [42]. A small, short-term study investigating the impact of WS supplementation on body weight

management in subjects under chronic stress reported a small, yet significant reduction compared with placebo (3.03% vs. 1.46%, respectively) and had a good safety profile [43].

Based on this solid pre-clinical data and the scant yet promising clinical evidence for the two compounds administered separately, it is tempting to speculate that an combination of the extracts of CC and WS may, on the one hand, act synergistically to favor weight loss in patients with overweight or obesity and, on the other hand, allow for the use of smaller dosages that will lead to the absence of side effects. The feasibility and safety of such an approach in humans is supported by previous clinical trials using either WS or CC to treat stress [44], cognitive dysfunction [45,46], pain [47], and the metabolic disturbances associated with polycystic ovary syndrome [12,48].

The aim of the present pilot study was to test, for the first time, whether an oral supplement containing CC and WS extracts yielded greater weight loss than placebo in patients with overweight and obesity undergoing a mildly hypocaloric dietary regime. Considering the rising incidence of obesity and the current unaffordability of anti-obesity drugs for a large proportion of overweight and obese patients, we feel that this study may provide an opportunity for a cheap and safe strategy to prevent and possibly counteract overweight and mild obesity.

2. Materials and Methods

2.1. Study Design

This was a multicenter, randomized (1:1), double-blind, placebo-controlled, cross-over, 4-week long study. To facilitate enrollment, 6 centers active in the treatment of obesity were recruited (i.e., 3 centers at Sapienza University of Rome, 1 center at Gemelli hospital of Rome, 1 private center in Rome, and 1 private center in Frosinone, LT, Italy). The leading center was the Department of Translational and Precision Medicine at Sapienza University, Rome. Adult (age range: 25–75 years) patients with overweight or obesity (BMI range: 26–35) referred at the participating clinics were screened for inclusion.

The patients were assessed at the beginning and end of each arm of the study, which lasted 4 weeks; the in-between wash-out period was 2 weeks. All patients received a mildly hypocaloric diet (i.e., −20% of the usual caloric intake as assessed by a 24 h dietary recall). The daily dietary intake included approximately 45–50% of calories from carbohydrates, up to 30% of calories from fat (<10% saturated fat) and 20–25% of calories from protein. Patients met individually with a dietician at each follow-up visit to assess compliance to the prescribed diet through a 24 h dietary recall. Physical activity was self-reported, and adherence was subjectively evaluated by the dietician at every visit.

The study was designed according to the principles of the Declaration of Helsinki and was approved by the Ethics Committee at Sapienza University of Rome (approval n. 5115). Written informed consent was obtained prior to the enrolment. This clinical trial was registered on ClinicalTrials.gov (NCT05210218).

2.2. Participants

The inclusion criteria were being overweight or obese based on BMI and a willingness to provide informed consent. Exclusion criteria were heart failure, congenital cardiomyopathies, episodes of tachy/bradyarrhythmia, acute myocardial infarction within 3 months from the enrollment, and inability or unwillingness to provide informed consent. Pregnant women were also excluded from the study.

2.3. Study Product

The study product, in a capsule formulation, was made using extracts of *Cinnamomum cassia* (CC) and *Withania somnifera* (WS) (300 mg + 150 mg, respectively) (Nutrintech Ltd., London, UK) and was to be taken three times a day. Each capsule contained both extracts. Each patient took the study product or placebo (i.e., the same amount of cellulose) during the two treatment arms, and the treatment order was randomized and double blinded. The allocation concealment was obtained thanks to the use of pre-packed numbered boxes

for each patient. All boxes were identical in appearance and the treatment and placebo capsules looked indistinguishable. Both investigators and patients were kept blinded to the treatment allocation throughout the clinical trial. The doses used in this trial were based on the studies by Borzoei et al. and Chengappa et al. [46,48]. Treatment compliance was assessed by accounting for unused medication brought back at each follow-up visit.

2.4. Outcome Measures

A thorough physical examination was conducted and a full medical history was recorded at each visit. Body weight and height were obtained between 8 and 10 AM in fasting subjects wearing light clothing and no shoes with an empty bladder at baseline and at every follow-up visit. A calibrated scale and stadiometer were used for all patients. Waist circumference was measured in the same instance at the midpoint between the lower rib margin and the iliac crest, the patients had their waist uncovered and were asked to stand with their feet close together and their weight equally distributed on each leg. Side effects were noted at the end of each arm.

2.5. Statistical Analysis

Data were analyzed by an independent blinded statistician (GN) through the use of STATA v. 14.1 (StataCorp. 2015. Stata Statistical Software: Release 14. StataCorp LP, College Station, TX, USA). The results are presented as mean +/− SE. The demographic and clinical characteristics are summarized by means of descriptive statistics (average, 95% confidence interval, median, and interquartile range) in the case of continuous variables and by means of absolute frequencies and percentages in the case of categorical variables. The comparison between the two treatments was carried out using the Z test for independent proportions, whereas the Mann–Whitney U test was used for the comparison of quantitative variables between the two groups. Differences were considered statistically significant when $p < 0.05$.

Based on the available literature, it was foreseen that the combination diet + CC/WS could lead to a weight loss of approximately 2–4 kg in 4 weeks, whereas the combination diet + placebo could lead to a loss of 1.5–2.5 kg. Based on this assumption, 35 patients were planned to be included in the present study, leading to a power of 80% with the statistical significance set at 0.05. Considering a possible drop-out rate of 20%, 43 patients were enrolled.

3. Results

3.1. Study Population

Forty-three patients were enrolled. Three patients dropped out during the study, two for personal reasons and one because of the development of abdominal discomfort at the end of the first 4 weeks. Forty patients completed the study and were analyzed, and their main clinical characteristics are summarized in Table 1. Briefly, the mean age was 46 years, 72% were female, mean BMI was 31 kg/m^2, mean weight was 87 kg, and mean waist circumference was 102 cm. Approximately one-third of the patients (34.9%) were classified as overweight and 65.1% as obese, of which 2.3% had severe obesity (BMI > 35).

Table 1. Baseline characteristics of the patients (N: number, BMI: body mass index; CI: confidence interval).

Parameter	% or Mean (95% CI)
N	40
Male (%)	27.9
Age (years)	46.1 (42.7–49.5)
Weight (kg)	86.97 (83.75–90.19)
Height (m)	1.663 (1.638–1.689)
BMI (kg/m^2)	31.35 (30.63–32.06)
Waist circumference (cm)	101.48 (98–104.96)
Waist circumference (cm) (female)	99.8 (95.33–104.28)
Waist circumference (cm) (male)	105.79 (8101.12–110.45)
Overweight (%)	34.9
Moderate obesity (%)	62.8
Severe obesity (%)	2.3

3.2. Safety and Tolerability

Minor adverse events were recorded in approximately 2% of the study population, the most common being gastro-esophageal reflux, constipation, and abdominal discomfort. No difference treatment-wise was observed. No major adverse events were recorded throughout the study. No difference in study compliance (as inferred from unused capsules brought back to follow-up) were observed between the placebo and CC/WS groups ($p = 0.37$).

3.3. Efficacy

Body weight loss was significantly greater when the hypocaloric diet was supplemented with CC/WS compared with placebo (−2.66% vs. −1.28%, respectively; $p = 0.0002$). Interestingly, the effect was more marked in patients with more excess weight, as those with obesity experienced a weight loss of 3.8% vs. 1.9% ($p = 0.0143$), as opposed to those with overweight, who had a mean weight loss of 2.8% vs. 0.9% ($p = 0.009$). When stratifying the results according to the period during which the supplement was received, the weight loss effect was greater when CC/WS was initiated simultaneously with the diet (i.e., first arm) and the placebo was taken subsequently (−3.3% vs. −1.7%, respectively; $p = 0.001$). When CC/WS was received in the second arm of the study, weight loss remained numerically greater than in the placebo group but lost its significance (−1.8% vs. 1%, $p = 0.11$) (Table 2).

Table 2. Anthropometric changes over time according to treatment arm.

	Week 4 CC/WS	**Placebo**	***p***	**Week 10 CC/WS**	**Placebo**	***p***
N	22	18		22	18	
BMI (kg/m^2)	29.94 (28.89–30.99)	31.29 (30.41–32.18)	0.0277	29.63 (28.52–30.74)	30.39 (29.46–31.33)	0.1404
Waist circumference (cm)	97.83 (93.62–102.05)	100.87 (95.36–106.38)	0.3715	96.19 (91.94–100.43)	96.53 (90.78–102.28)	0.9695
Weight change compared with baseline (%)	−3.3 (−4.0–−2.6)	−1.7 (−2.2–−1.1)	0.001	−0.98 (−1.67–−0.28)	−1.78 (−2.57–−1.00)	0.1122
Waist circumference change compared with baseline (cm)	−2.75 (−3.87–−1.62)	−1.73 (−3.44–−0.02)	0.0307	−1.39 (−2.60–−0.18)	−2.64 (−3.75–−1.53)	0.239
Waist circumference change compared with baseline (cm) (female)	−2.58 (−4.13–−1.04)	−2.10 (−4.47–0.25)	0.3168	−1.02 (−2.64–0.58)	−2.46 (−3.85–−1.06)	0.3863
Waist circumference change compared with baseline (cm) (male)	−3.14 (−4.78–−1.50)	−0.70 (−1.53–0.13)	0.0108	−2.28 (−4.11–−0.45)	−3.25 (−5.96–−0.53)	0.3863

p is from a Z-test or Mann–Whitney U test as appropriate. Significant values are highlighted in bold. N, number; BMI, body mass index; CC, cinnamon; WS, *Withania somnifera.*

Waist circumference was significantly reduced in patients receiving CC/WS when compared with the placebo group (−2.75 cm vs. −1.73 cm, i.e., −2,8% vs. 1,7%, respectively; $p = 0.03$) at 4 weeks. Stratification by gender showed that male subjects had a significant reduction (−3.14 vs. −0.7 cm $p = 0.01$), whereas female patients did not show a significant improvement compared with placebo ($p = 0.3$). When CC/WS was consumed after placebo, no difference in waist circumference reduction was observed compared with placebo ($p = 0.24$) (Table 2).

4. Discussion

Our study demonstrates that the combination of extracts of *Cinnamomum cassia*, also known as Chinese cassia or Chinese cinnamon, and *Withania somnifera*, also known as Ashwagandha or winter cherry, enhances weight loss in overweight or obese patients receiving a hypocaloric diet when compared with placebo without causing significant side effects. The weight loss effect appears more pronounced when the combination is prescribed when beginning the hypocaloric diet than when it is prescribed weeks after starting the diet. This could be explained by higher baseline BMI, a factor known to positively impact weight loss, as has already been observed in similar studies [49]. Moreover, the kinetics of WS and CC in human subjects is not entirely elucidated; a 2-week washout period might have not been enough, possibly leading to a confounding effect in those switching from CC/WS

to placebo. When compared with the results obtained by cinnamomum supplementation in other clinical trials [50], it appears that the weight loss obtained by our combination of CC/WS is greater.

The CC/WS treatment yielded a significant reduction in waist circumference in male patients but not female patients. This could be explained by the different distribution of adipose tissue in males vs. females. The latter mainly have fat deposition at the level of the hip circumference and any change in this region will not be captured by measuring the waist circumference.

It could be also postulated that the tested extracts were associated with significant weight loss due to changes induced in the gut microbiota, since both cinnamon and *Withania somnifera* have antimicrobial activity.

Of great interest, the combination at the doses given in this trial is effective in both overweight patients and patients with obesity, highlighting its potential role for a large section of the population. The strengths of this study are in its methodological design, the power calculation, the analysis being performed independently from the researcher, and the collection of the data via a database in the cloud with rigorously monitored access. The size of the effects of the combination of these agents is quite remarkable. In fact, during the first 4 weeks of treatment weight loss was 3.3%, which is similar to the weight loss observed with pharmacotherapy.

Cinnamomum is a plant genus that includes >200 species, including *Cinnamomum cassia*, all originating from the same tropical and subtropical Asian regions. Cinnamomum species differ in their content of active components [51], yet their differential clinical activity for weight loss has never been tested in clinical trials.

Some limitations of the study should also be acknowledged. This was not a mechanistic study; therefore, it was not possible to elucidate the mechanisms involved in the weight loss effect. Additionally, our study focused on weight loss, and outcome measures, including biochemical indices, were kept to a minimum. The sample size was relatively small; however, an a priori sample size calculation was conducted.

Nevertheless, in conclusion, our study demonstrates, for the first time, that the tested combination is a cheap yet effective strategy to enhance weight loss in overweight and obese patients receiving a hypocaloric diet. Further studies are warranted to investigate the mechanisms underlying the weight loss effect of CC/WS in human subjects, as well as to explore the potential additional metabolic effects obtained with this treatment.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Sapienza University (protocol code 5115; 13 September 2018).

Data Availability Statement: Data is unavailable due to privacy restrictions.

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