Short Research Article

Title: A Randomized, Double-Blind, Placebo-Controlled Study of a Blend of Herbal Extracts Taken Once Per Day for Weight Loss in Healthy Volunteers

ABSTRACT

Aims: We previously demonstrated that a blend of herbal extracts (Weighlevel®; a mixture of extracts from the leaves of *Alchemilla vulgaris*, *Olea europaea*, *Mentha longifolia* and from the seeds of *Cuminum cyminum*) taken 3 times per day is effective in producing weight loss in both preclinical and clinical studies. However, medication compliance tends to decrease as the number of daily doses increases. Thus, a once per day formulation is preferable for consumer ease of use. The aim of the present study was to test the efficacy of a new slow-release formulation (Weighlevel® One) taken once per day on change in body weight and related measures.

Study design: Randomized, double-blind, placebo-controlled study.

Place and Duration of Study: Health Clinics in Copenhagen, Denmark between 7 January 2016 and 5 March 2016.

Methodology: Thirty-six adult subjects were randomized to consume the herbal blend (n = 20) or placebo (n = 16) once per day for 8 weeks. Weight and waist circumference were assessed weekly. Weekly follow-up reports were conducted online. In person visits occurred at baseline and at weeks 4 and 8.

Results: After 8 weeks, the herbal blend group lost an average of 3.7 kg (95% CI of 3.0 to 4.5 kg); whereas the placebo group lost 0.1 kg (95% CI of -0.7 to 1.0 kg). This difference in mean weight loss between the herbal blend and placebo groups was statistically significant (P <.001). Significant reductions in waist circumference were also observed (P <.001). The herbal blend was well tolerated. No adverse events or changes in wellbeing were reported.

Conclusion: Daily administration of this blend of herbal extracts may help persons with overweight or obesity lose weight.

Keywords: Alchemilla vulgaris, Olea europea, Mentha longifolia, Cuminum cyminum, overweight, obesity, slow release

Comment [W1]: ITALIC

1. INTRODUCTION

Obesity rates worldwide have nearly tripled over the last four decades [1]. The World Health Organization estimates that nearly 2 billion adults are currently overweight or obese [1]. Sustained weight loss of as little as 3% to 5% can produce clinically meaningful reductions in cardiometabolic risk factors such as blood glucose and lipids, with larger weight losses producing greater benefits [2]. However, many people struggle to lose weight through diet and exercise alone.

Some plants used in traditional Greco-Arab and Islamic medicine have properties which may aid in weight loss. *Alchemilla vulgaris* (Lady's mantle) is used in traditional Arabic medicine for weight loss and to treat stomach and intestinal pain [3]. It also has anti-inflammatory properties [4]. *Olea europea* (olive) improves insulin sensitivity and may reduce blood pressure and plasma lipids [5-7]. *Mentha longifolia* (wild mint) is traditionally used to treat gastrointestinal disorders and also has antimicrobial properties [8]. Supplementation with *Cuminum cyminum* (cumin) has been reported to produce weight loss in overweight subjects [9].

We previously demonstrated that a blend of herbal extracts (Weighlevel®; a mixture of extracts from the leaves of *Alchemilla vulgaris*, *Olea europaea*, and *Mentha longifolia* and from the seeds of *Cuminum cyminum*) taken 3 times per day is effective in producing weight loss in both preclinical and clinical studies [10, 11]. However, the rate of medication compliance tends to

decrease as the number of daily doses increases. A systematic review found that medication compliance dropped to 65% for medications taken 3 times per day, and compliance was significantly higher for once daily regimens [12]. This suggests that patients would be more likely to consume the herbal blend as instructed if the dosing regimen were once daily rather than 3 times per day.

The aim of the present study was to test the efficacy of a new slow-release formulation (Weighlevel® One) taken once per day in a randomized, double-blind, placebo-controlled study. We hypothesized that the new herbal blend formulation would produce incremental and sustained weight loss over the course of the 8-week study.

2. MATERIAL AND METHODS

2.1 Participants

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Participants were recruited by a specially trained qualified nurse (Erla Øregaard, who is a recognized as a specialist in patient safety by the Danish Health Authority) from Health Clinics in Copenhagen, Denmark between 7 January 2016 and 5 March 2016. Informed consent was obtained from all participants prior to participation in the study. Eligible participants were generally healthy, not pregnant, were unsatisfied with their current weight, interested in losing weight, and agreed to follow the study protocol.

2.2 Study Design

This study was a randomized, double-blind, placebo-controlled trial. Participants were randomized to receive either 1 tablet of herbal blend or 1 tablet of placebo per day for 8 weeks. Herbal blend and placebo tablets were provided free of charge. The herbal blend (Weighlevel®One) is a mixture of extracts from the leaves of *Alchemilla vulgaris*, *Olea europaea*, Mentha longifolia and from the seeds of *Cuminum cyminum* and a patented slow release component (Propol®). These ingredients are Generally Regarded as Safe (GRAS). The matching placebo and herbal blend each had a net weight of 0.88 grams and were manufactured by ProPharma (Copenhagen). Treatment allocation was concealed, and blinding was maintained by administering the herbal blend or placebo in coded containers. The participants, recruiting nurse, and investigators remained blinded during the study.

Participants were instructed to take 1 tablet in the morning and to maintain their daily eating or exercise routine. Body weight and waist circumference measurements were obtained at the same time and week-day throughout the study. Weekly follow-up reports were conducted online. In person visits occurred at baseline and at Weeks 4 and 8. Adverse events were assessed throughout the study.

2.3 Visual Analog Scale Assessments

Appetite, craving for sweets, and bowel health were assessed using visual analog scales (VAS) which have been reported to be reliable in appetite research [13]. Each visual analog scale consisted of a clear unmarked plastic strip. Participants were asked to place their finger on the strip in response to the following questions: How hungry are you today? (appetite), How much have you been craving sugar/sweets today? (craving), and Are you having bowel movements daily/how does your bowel feel? (bowel health). Each plastic strip was then given a numerical

rating from 1 to 5 by the investigator in which higher numbers indicated an improvement: Appetite (1=hungry, 5=no appetite), Craving (1=craving sugar, 5= no craving), Bowel Health (1=infrequent bowel movements, uncomfortable bowel, 5=bowel ok).

2.4 Statistical Analysis

All results reported are for the Intent-to-Treat Population. Missing values for the 4 subjects that dropped out of the study early are accounted for by maximum likelihood, using a missing at random (MAR) assumption. A repeated-measures mixed-effects model was used to compare changes from baseline in treatment and control groups. A random subject effect and fixed treatment, baseline value and time effects were included in the model.

3. RESULTS

3.1 Participants

A total of 50 volunteers were assessed for eligibility. Reasons for exclusion from the study were: did not meet inclusion criteria (n=14) and declined to participate (n=4). Thirty-six participants were randomized to receive either 1 tablet of herbal blend (n=20) or 1 tablet of placebo (n=16) per day for 8 weeks. Four participants (3 women and 1 man) dropped out after randomization and before the first weekly online follow-up visit. Demographics and baseline characteristics were similar for the 2 treatment groups (see Table 1).

Table 1. Demographics and baseline characteristics

	Placebo (N=16)	Herbal Blend (N=20)
Age (years)	47.1 (9.8)	45.3 (9.1)
Sex, Female	14 (87.5%)	19 (95.0%)
Weight (kg)	79.2 (10.0)	79.1 (15.2)
Height (cm)	171.9 (6.2)	170.8 (7.9)
BMI (kg/m^2)	26.8 (3.5)	27.1 (4.4)
Waist circumference (cm)	91.4 (8.6)	93.4 (12.1)

* Data are mean (SD) or n (%)

3.2 Body Weight and Waist Circumference

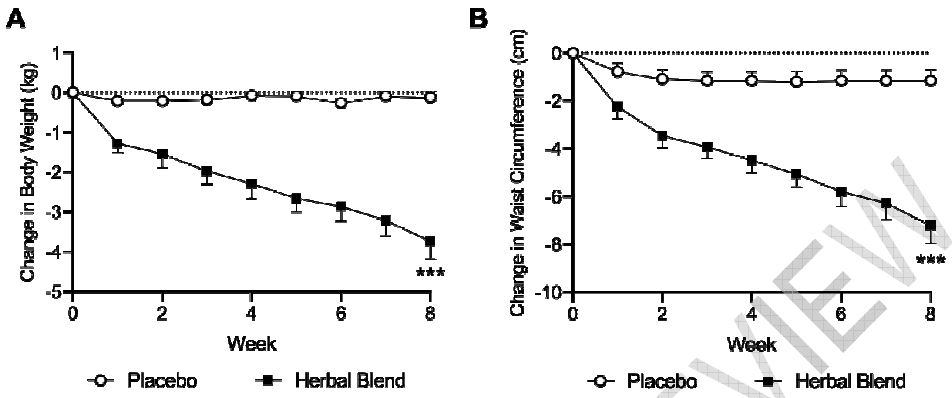
After 8 weeks, the herbal blend group lost an average of 3.7 kg (95% CI: 3.0 to 4.5 kg; *P* <.001) compared with 0.1 kg lost for the placebo group (95% CI: -0.7 to 1.0 kg) (Table 2). This was equivalent to a 4.7% reduction in weight in the group that received the herbal blend, compared to a 0.2% reduction in the placebo group (Table 2, *P* <.001). The group that was treated with the herbal blend demonstrated continued weight loss that was sustained for the duration of the 8-week study (Figure 1A), with mean weight loss of 0.46 kg per week. In contrast, mean weight loss in the placebo group was generally unchanged from baseline. Waist circumference was also reduced by 7.2 cm in the herbal blend group compared with a reduction of 1.2 cm in the placebo group (Figure 1B and Table 2, *P* <.001).

Table 2. Change from baseline to Week 8 in weight, waist circumference, and visual analog scale ratings

Change	Placebo (N=16)	Herbal Blend (N=20)	LS Mean Difference	*P* value
Body Weight (kg)	-0.1 (0.4)	-3.7 (0.4)	-3.6 (0.6)	*P* <.001
95% CI	[-1.0, 0.7]	[-4.5, -3.0]	[-4.7, -2.5]	
Body Weight (%)	-0.2 (0.4)	-4.7 (0.3)	-4.5 (0.5)	*P* <.001
95% CI	[-1.0, 0.7]	[-5.7, -4.0]	[-5.7, 3.4]	
Waist Circumference (cm)	-1.2 (0.8)	-7.2 (0.6)	-6.1 (1.0)	*P* <.001
95% CI	[-2.7, 0.4]	[-8.5, -5.9]	[-8.1, -4.0]	
VAS Appetite	-0.4 (0.2)	0.6 (0.1)	1.0 (0.2)	*P* <.001
95% CI	[-0.7, 0.0]	[0.3, 0.9]	[0.5, 1.4]	
VAS Cravings	-0.2 (0.3)	0.9 (0.2)	1.2 (0.3)	*P* <.001
95% CI	[-0.8, 0.3]	[0.5, 1.4]	[0.5, 1.9]	
VAS Bowel Health	-0.5 (0.3)	0.3 (0.3)	0.9 (0.4)	*P* =.002
95% CI	[-1.2, 0.1]	[-0.2, 0.9]	[0.0, 1.7]	

* Data are least-squares mean (SE) and 95% confidence interval. VAS = visual analog scale.

Figure 1. Herbal blend reduced body weight and waist circumference

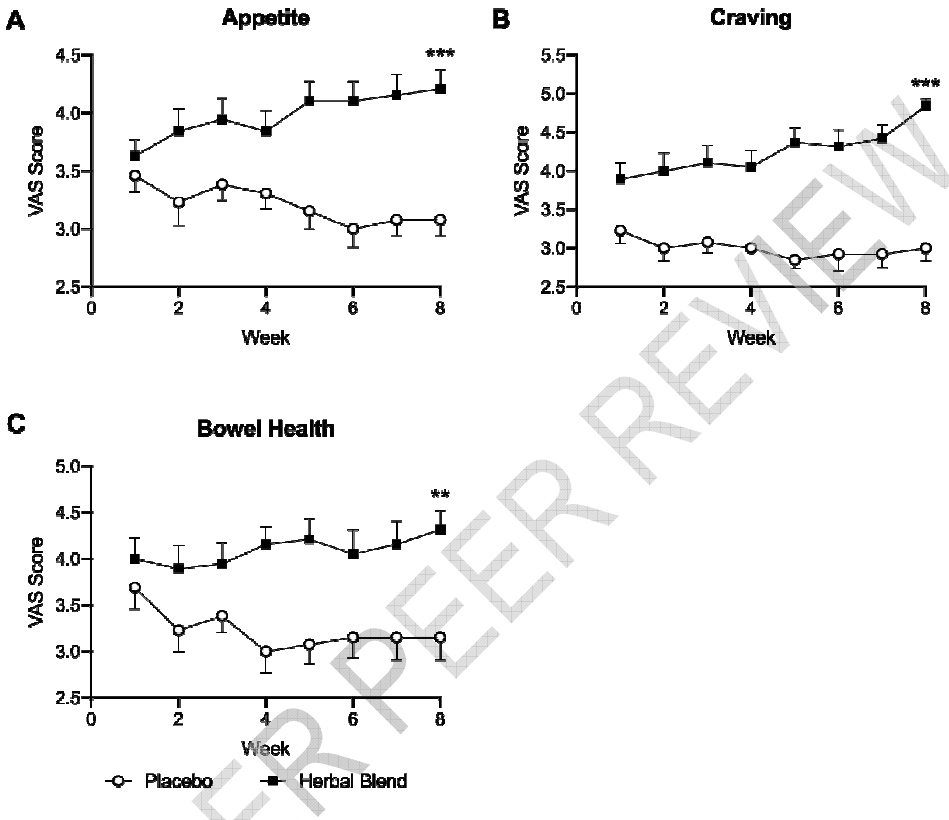


A) Change in body weight. Mean baseline body weight was 77.9 kg for the placebo group and 78.1 kg for the herbal blend group. B) Change in waist circumference. Mean baseline waist circumference was 91.2 cm for the placebo group and 93.0 cm for the herbal blend group. Data are mean ±SE (n=16-20). ***P <.001 compared to placebo.

3.3 Visual Analog Scale Assessments

Statistically significant improvements in patient-reported appetite, craving for sweets, and bowel health were observed compared to placebo at Week 8 (all P <.01, Table 2 and Figure 2). These improvements in patient-reported appetite and craving for sweets in the herbal blend group continued for the duration of the study whereas there was a slight worsening in the placebo group (Table 2 and Figure 2A and B). Bowel health also appeared to worsen in the placebo group, compared to an improvement in the herbal blend group (Table 2 and Figure 2C).

Figure 2. Herbal blend improves subjective ratings of appetite, craving and bowel health



Increases in score demonstrate improvements. A) Visual analog scale rating of appetite (1=hungry, 5=no appetite). B) Visual analog scale rating of craving for sweets (1=craving sugar, 5= no craving). C) Visual analog scale rating of bowel health (1=infrequent bowel movements, uncomfortable bowel, 5=bowel ok). Data are mean ±SE (n=16-20). $^{**}P < .01$, $^{***}P < .001$ compared to placebo. VAS = visual analog scale.

3.4 Safety

The herbal blend was well tolerated. No adverse events or changes in wellbeing were reported.

4. DISCUSSION

The results presented here demonstrate that the slow-release herbal blend taken once per day produced statistically significant weight loss in healthy adults. After 8 weeks of treatment, participants in the herbal blend group lost an average of 4.7% of their baseline body weight compared with 0.2% weight loss in the placebo group. The herbal blend was also well tolerated and there were no safety concerns. This is in agreement with previous studies where the herbal blend was administered 3 times per day and produced weight loss of approximately 7% after 2 months of treatment and 10-13% weight loss after 3 months [10, 11]. The weight loss observed with the once per day formulation was slightly lower than previously observed with the 3 times per day formulation. This difference may be related to the higher mean baseline body weight of participants in previous studies. It may also be related to differences between populations where previous studies were performed (Galilee, Israel) and where the current study was performed (Copenhagen, Denmark).

In addition to weight loss, participants also experienced a statistically significant reduction in waist circumference that corresponded with the reduction in body weight. Whether the reductions in body weight and waist circumference (both measures of the metabolic syndrome) reflect an improvement in other weight-related comorbidities, such as lipids, blood pressure, and blood glucose remains to be determined. However, the improvement in body weight approaches a 5% reduction from baseline, which has been determined to represent clinically meaningful weight loss that reduces the incidence of diabetes, reduces blood pressure, and improves lipids.[14]

Compared to placebo, participants also reported improvements in appetite, craving, and bowel health, measured by VAS, which has demonstrated efficacy in assessing appetite.[13] These improvements were observed in the context of weight loss and the reductions in appetite and

craving may contribute to the mechanism for weight loss. The improvement in bowel health is also notable, given that fecal incontinence is common in individuals with obesity.[15]

5. CONCLUSION

In summary, the 4.7% weight loss in participants treated with the herbal blend was statistically significant and well within the range that would be expected to produce beneficial effects on markers of cardiometabolic risk [2]. The ease of use of a once per day formulation is expected to improve adherence and provide meaningful improvements in weight-related health.

Competing Interests

The author declares that no competing interests exist.

Consent

Informed consent was obtained from all participants prior to participation in the study.

Ethical approval

All experiments were examined and approved by the appropriate ethics committee represented by professor, dr. med Steen Lindkær-Jensen (Aarhus University, Aarhus, Denmark and Imperial College, London, UK), and were examined and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we

do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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