A Double Blinded- Randomized Clinical Study with "Weighlevel", a Combination of Four Medicinal Plants Used in Traditional Greco-Arab and Islamic Medicine

Omar Said[*,1,2], Khaled Khalil[1], Stephen Fulder[1], Yousaf Marie[1], Eli Kassis[4] and Bashar Saad[*,2,3]

[1]*Antaki Center for Herbal Medicine Ltd. Kfar Kana 16930, P.O. Box 2205 Israel*

[2]*Qasemi Research Center- Al-Qasemi Academic College, Baga Algharbiya, Israel*

[3]*Faculty of Art and Sciences, The Arab American University Jenin, P.O. Box 240, Jenin, Palestine*

[4]*Sprunk-Jansen, A/S Strandvejen 100, 2900 Hellerup Denmark*

Abstract: Weighlevel, is a mixture of extract of leaves of *Alchemilla vulgaris*, *Olea europea* and *Mentha longifolia* L, as well as seeds of *Cuminum cyminum*. These plants are used in traditional Greco-Arabic and Islamic medicine as well as in European herbal medicine. Weighlevel has been recently found to be safe and effective in weight loss in preclinical *in vitro* and *in vivo* studies, including a preliminary, uncontrolled human trial. Here we report the results of our randomized, double blinded, placebo controlled clinical study. The tests were carried out among 34 human volunteers. The test group included 19 volunteers whereas the control group included 15 volunteers who consumed Weighlevel tablets or placebo tablets 1 x 3 daily, respectively. All 34 subjects were asked to continue their usual diet, except for strictly limiting food intake to 3 main meals per day without snacking, and to take one Weighlevel tablet or placebo tablet 30 minutes before each meal. Five subjects were excluded (three from the test group and two from the control group) due to absence from scheduled visits. Twenty-nine subjects were evaluated for efficacy and tolerability of Weighlevel every month for 3 months. Weighlevel was well tolerated by all subjects and no side effects were reported. After 12 weeks, test subjects, on average, showed statistically significant weight loss and body mass index (BMI) reductions. Weight and BMI changes for the placebo group were not statistically significant. Results indicate safety, tolerability, and efficacy of Weighlevel in weight loss.

Keywords: *Alchemilla vulgaris*, *Olea europea*, *Mentha longifolia*, *Cuminum cyminum*, Greco-Arab medicine, overweight, obesity.

INTRODUCTION

Overweight and obesity are major health challenges in the Arab world, as well as in Western world, and are associated with serious clinical complications. Available conventional therapy of these conditions is limited to anorexics such as amfepramon and sibutramin and one malabsorptive drug, orlistat. Side effects associated with these therapies limit their usefulness.

Effective management of weight will be furthered if modern science can utilize safe plants derived from ancient medical systems such as Greco-Arab and Islamic medicine, Ayuvadic, and Chinese medicines. Remedies used by these traditional medicines can fill the gap and supplement currently employed medicines. Mild overweight was generally accepted in ancient Arab societies and considered a reflection of a high socioeconomic level and part of the desired beauty standards in those days. Therefore, limited anti-obesity remedies were discovered compared to other medical fields. Only severe obesity was considered suitable for treatment using specific medicinal plants, body exercises and control of food consumption [1-3]. Nevertheless, based on our ethnobotanical surveys and on medical knowledge obtained from ancient Greco-Arab and Islamic script, we prepared a mixture of four plants. "Weighlevel" is composed of *Cuminum cyminum L.* (Cumin), *Mentha longifolia L* (sorting menthe) and *Olea europaea L.* (olive) leaf, which are all classed as foods or spices throughout Europe and are taken in large amounts while *Alchemilla vulgaris L.* (lady's mantle) is regarded as safe by the German Commission even at large doses without known adverse effects [4-7]. Deeply rooted in Arabic medicine, *Alchemilla vulgaris* L. has been used for treating obesity, gastrointestinal pain, and inflammation [8, 9]. Olive leaves are a typical herbal remedy of the Arab-Islamic world and reported to possess hypoglycaemic, hypotensive-diuretic and antioxidant properties [7, 10-12]. Mint as well as cumin has been used to reduce appetite [8] and to improve digestion by relieving digestive symptoms

*Address correspondence to these authors at the Antaki Center for Herbal Medicine Ltd. Research and Development Regional Center - The Galilee Society, P.O. Box 2205, Kfar Kana 16930, Israel; Fax: 0097246412713; E-mail: omar@al-antaki.com, osaid@gal-soc.org, bsaad@gal-soc.org

1876-391X/10

such as pain, spasm, gas, and dyspepsia and creating a sensation of fullness [13].

Recently, Weighlevel was found to exhibit high levels of safety as measured *in vitro* and in animal tests [14]. The LD50 value of Weighlevel was 15.3 g/kg which would correspond to more than a kilogram in human. Similar results were seen in *in vitro* studies by measuring the LDH release where no significant change in LDH-release was found whether as a function of increasing the Weighlevel concentrations or as a function of increasing the incubation period. In addition, Weighlevel at a concentration of 50 mg/ml significantly reduced MDA-release from 0.89 ± 0.05 to 0.28 ± 0.03 nM/mg proteins. Furthermore, Weighlevel was tested in a 3-month uncontrolled human trial and was well tolerated in all 66 subjects, with no minor or major adverse effect noted by any of them [14]. Significant and progressive weight reductions were observed each month averaging 1 kg/week over 3 months. Average weight was reduced from baseline of 90.5 ± 1.2 kg to 78.5 ±1.4 kg at 3 months ($p < 0.0005$). Subjects' average BMI was reduced after three months from 28.5 ± 1.2 kg/m² and 32.1 ± 1.8 kg/m² to 24.5 ± 1.4 kg/m² and 27.5 ± 2.2 kg/m² in overweight and obese group, respectively. No significant effects were seen in the control group who was asked to restrict it to 3 main meals. In our present randomized, double blind, placebo controlled study we continued or efficacy evaluations of Weighlevel.

MATERIAL AND METHODS

The leaves of lady's mantle, olive and wild mint, as well as the seeds of cumin were collected from the Galilee region, dried under shade, and powdered to a fine grade as extracts by Antaki Ltd.-laboratories, Kfar Cana, Israel. Weighlevel tablets (310 mg/tablet) were prepared at Karmat Micro Encapsulation laboratories, Kibbutz Ramot Menashe, Israel.

Table 1. Basic Data of the 29 Volunteers Participated in the Double Blinded-Randomized Clinical Study, Including Age (Years), Gender, Weight (kg) BMI (kg/m²), and Length (m)

Patient no	Age	Gender	Weight	BMI	Height
1	41	Male	108	33.71	1.79
2	32	Female	87	30.82	1.68
3	41	Male	103	32.51	1.78
4	40	Female	89	29.74	1.73
5	19	Male	88	30.81	1.69
6	28	Female	92	31.10	1.72
7	38	Male	99	33.08	1.73
8	40	Female	91	29.71	1.75
9	25	Female	74	27.18	1.65
10	35	Male	102	33.69	1.74
11	31	Male	98	29.59	1.82
12	20	Male	96	30.99	1.76
13	39	Female	91	30.41	1.73
14	37	Female	94	33.30	1.68
15	40	Female	90	27.78	1.8
16	29	Male	94	32.15	1.71
17	44	Female	89	30.80	1.7
18	52	Male	108	34.87	1.76
19	23	Female	91	31.86	1.69
20	36	Female	103	35.22	1.71
21	29	Male	95	31.02	1.75
22	33	Female	88	31.55	1.67
23	41	Female	79	29.02	1.65
24	50	Male	99	30.56	1.8
25	28	Female	91	30.76	1.72
26	34	Male	98	31.64	1.76
27	24	Male	94	32.91	1.69
28	46	Male	104	36.41	1.69
29	47	Female	84	25.36	1.82
AVG	**35.24**		**93.8**	**31.3**	**1.7**
STD	**8.696**		**7.918**	**2.380**	**0.048**

Each tablet contained *60 mg Alchemilla vulgaris L., 50 mg Olea europaea L., 20 mg Mentha longiforia L, 25 mg Cuminum cyminum L., 7 mg Vitamin C, and 148 mg Tricalcium phosphate (TCP)* [14].

Clinical Investigations

Human volunteers (n=34, ages: 19-52, women and men) were selected on the basis of routine visits to Antaki center clinic in Galilee, under the supervision of Dr. Yousaf Marie, and were asked if they were willing to take a herbal therapy for weight loss. After a thorough explanation of Weighlevel-components, they were asked to take one tablet of Weightlevel or one tablet of placebo half an hour before each of three daily meals, with two cups of water. The 34 subjects recruited into the study had an average age of 35.2 ± 8.7 (range 19-52) years. They had an average weight of 93.8 ± 7.9 kg and an average height of 173 ± 4.8 cm, corresponding to an average BMI of 31.3 ± 2.4 kg/m². Women composed 51.7% of subjects with an age range of 23-47 years. Almost 23% of all subjects were on some medications mainly for ischemic heart disease, diabetes mellitus and/or hypertension. All medications were kept unchanged during the study period as patients were in a stable clinical condition.

The 34 subjects were randomized into two groups. Five subjects were subsequently excluded as they violated the protocol, due to absence from scheduled visits. Efficacy and tolerability is given for the remaining 29 subjects. Human volunteers were asked to continue their daily activities and habits, especially their food-intake, but to restrict it to 3 main meals and to remember to take one tablet of Weighlevel/ placebo 30 minutes before each meal. All usual medications were kept unchanged during the study period of 3 months. Informed consent was obtained from each subject. Each subject was given a free-of-charge box containing 90 tablets of Weighlevel or placebo. At the beginning of the study, subjects visited Antaki center clinic for baseline measurements of height, weight, and blood pressure. The next visit was scheduled for 4 weeks later. The same measurements were taken, and subjects were asked to return the Weighlevel or placebo box so that returned tablets could be counted as a measure of patient compliance with the protocol. The same procedures were followed during two subsequent clinic visits, with a month between visits. Careful investigations of well being and of any adverse effect were undertaken by physicians at each clinic visit, throughout the trial.

STATISTICS

The Wilcoxon signed-rank test was used. Comparisons between groups were performed by the Wilcoxon rank-sum test. A 0.05 level of significance was set. Data obtained was expressed as a mean ± standard error of mean (SEM).

RESULTS

Weighlevel was well tolerated in all 29 subjects who completed the trial. No minor or major adverse effects were reported (Table **1**). Weighlevel was well tolerated with other

Table 2. Efficacy of Weighlevel in Reducing Weight (in kg) in the Test Group (n= 16 subjects). Significant and Progressive Weight Reductions were Observed each Month in the Test Group, which is Around 0.8 kg/Week over 3 Months. The Weight was Reduced from Baseline of 93.5 ± 7.9 kg to 84 ± 9.8 kg at 3 Months (p ‹ 0.0005). W0: at Start Time of the Study, W1: after one Month, W2: after Two Months, and W3: after Three Months. The Height of the Volunteers is given in Meter. (*) Indicate Significance Against both W0 and Previous Month

Patient no	Age	Gender	Weight				Patients height
			W0	W1	W2	W3	
1	41	Male	108	104	100	97	1.79
2	32	Female	87	85	83	81	1.68
3	41	Male	103	99	96	92	1.78
4	40	Female	89	87	87	86	1.73
5	19	Male	88	83	79	75	1.69
6	28	Female	92	87	84	79	1.72
7	38	Male	99	99	98	98	1.73
8	40	Female	91	87	83	78	1.75
9	25	Female	74	69	66	61	1.65
10	35	Male	102	97	94	88	1.74
11	31	Male	98	93	90	87	1.82
12	20	Male	96	91	87	84	1.76
13	39	Female	91	85	80	76	1.73
14	37	Female	94	93	93	93	1.68
15	40	Female	90	84	79	76	1.8
16	29	Male	94	94	94	93	1.71
AVG	33.44		93.5	89.81*	87.06*	84*	1.735
STDEV	7.429		7.9	8.3	8.8	9.8	0.05

Table 3. Effects of Weighlevel on BMI in the Test Group (n= 16 Subjects) Using Body Weight Index (BMI). A Progressive and Significant Weight Loss was seen in these Subjects During the whole Study Period. The BMI was Reduced after Three Months from 31± 1.97 kg/m² to 27.9 ± 3.09 kg/m². W0: at Start Time of the Study, W1: after One Month, W2: after Two Months, and W3: after Three Months. The Height of the Volunteers is Given in Meter. (*) Indicate Significance Against both W0 and Previous Month

Patient no	Age	Gender	BMI				Patients height
			W0	W1	W2	W3	
1	41	Male	33.7	32.5	31.2	30.3	1.79
2	32	Female	30.8	30.1	29.4	28.7	1.68
3	41	Male	32.5	31.2	30.3	29	1.78
4	40	Female	29.7	29.1	29.1	28.7	1.73
5	19	Male	30.8	29.1	27.7	26.3	1.69
6	28	Female	31.1	29.4	28.4	26.7	1.72
7	38	Male	33.1	33.1	32.7	32.7	1.73
8	40	Female	29.7	28.4	27.1	25.5	1.75
9	25	Female	27.2	25.3	24.2	22.4	1.65
10	35	Male	33.7	32	31	29.1	1.74
11	31	Male	29.6	28.1	27.2	26.3	1.82
12	20	Male	31	29.4	28.1	27.1	1.76
13	39	Female	30.4	28.4	26.7	25.4	1.73
14	37	Female	33.3	33	33	33	1.68
15	40	Female	27.8	25.9	24.4	23.5	1.8
16	29	Male	32.1	32.1	32.1	31.8	1.71
AVG	33.44		31.03	29.82*	28.91*	27.91*	1.735
STDEV	7.43		2.0	2.4	2.70	3.1	0.05

medica-tions for diabetes mellitus, hypertension, cholesterol and ischemic heart disease.

A significant and progressive weight reduction was observed each month in the test group (Table **2**), with an average of around 0.75 kg/week over 3 months. The average weight was reduced from baseline of 93.5 ± 7.9 kg to 84 ± 9.8 kg at 3 months ($p < 0.0005$). Similarly, a progressive and significant weight loss was seen in the BMI which was reduced after three months from 31± 1.97 kg/m² to 27.9 ± 3.09 kg/m² (Table **3**). No significant effects were seen in the placebo control group (Table **4** and Table **5**).

DISCUSSION

The present study evaluated Weighlevel, a combination of four herbal remedies that are traditionally known for their weight reduction effects. The Weighlevel combination contained 60mg *Alchemilla vulgaris L.*, 50mg *Olea europaea L.*, 20mg *Mentha longiforia L*, 25mg *Cuminum cyminum L.*, 7mg Vitamin C, and 148mg *Tricalcium phosphate* (TCP). The present study was conducted to build upon earlier evidence suggesting that Weighlevel is a safe and effective means to reduce body weight. The safety of Weighlevel was demonstrated previously in pre-clinical studies, including an LD50 assay in rats and *in vitro* testing using MTT and LDH assays [14]. A preliminary, uncontrolled human trial also showed that Weighlevel was well tolerated and, furthermore, suggested that it was effective for weight loss [14].

In the uncontrolled human trial, Weighlevel was safe and well tolerated by all 66 subjects and was therapeutically efficient, as weight loss in each subject was incremental and steady throughout the study period of 3 months. None of the subjects reported minor or major adverse effects, and subjects lost a remarkable average of 12 kg after 3 months [14]. All subjects in the uncontrolled trial ingested one Weighlevel tablet, three times daily, before meals. Subjects were instructed not to change their diets, except for limiting food intake to three meals, with no snacking between meals.

The same administration and food intake were followed in the present study. However, the present study included a control group, which received a placebo. The results from the present randomized, double-blind, controlled study were similar to those results from the previous uncontrolled trial. Compared to baseline, test subjects in the present study experienced a statistically significant average weight loss of 9.5 kg after 3 months. Placebo subjects experienced no statistically significant decreases in weight. The reduction in the extent of weight loss obtained in the present study compared with the previous uncontrolled one can be explained by the "placebo effect". These finding may

Tables 4. Efficacy of Placebo in Reducing Weight (in kg) in the Control Group (n= 13 Subjects). No Significant Weight Reductions were Observed after Three Months in this Group. W0: at Start Time of the Study, W1: after One Month, W2: after Two Months, and W3: after Three Months. The Height of the Volunteers is Given in Meter

Patient no	Age	Gender	Weight in Kg				Patients height (m)
			W0	W1	W2	W3	
1	44	Female	89	89	88	88	1.7
2	52	Male	108	106	108	106	1.76
3	23	Female	91	90	90	89	1.69
4	36	Female	103	105	104	104	1.71
5	29	Male	95	96	96	95	1.75
6	33	Female	88	88	86	86	1.67
7	41	Female	79	78	77	76	1.65
8	50	Male	99	100	101	101	1.8
9	28	Female	91	91	90	89	1.72
10	34	Male	98	97	97	98	1.76
11	24	Male	94	93	92	93	1.69
12	46	Male	104	105	104	103	1.69
13	47	Female	84	85	85	85	1.82
AVG	37.5		94.1	94.1	93.7	93.3	1.7
STDEV	9.9		8.3	8.5	9.0	8.9	0.051

Tables 5. Efficacy of Placebo in Reducing Weight (BMI) in the Control Group (n= 13subjects). No Significant Weight Reductions were Observed after Three Months in this Group. W0: at Start Time of the Study, W1: after One Month, W2: after Two Months, and W3: after Three Months. The Height of the Volunteers is Given in Meter

Patient no	Age	Gender	BMI -				Patients height
			W0	W1	W2	W3	
1	44	Female	30.8	30.8	30.4	30.4	1.7
2	52	Male	34.9	34.2	34.9	34.2	1.76
3	23	Female	31.9	31.5	31.5	31.2	1.69
4	36	Female	35.2	35.9	35.6	35.6	1.71
5	29	Male	31.0	31.3	31.3	31.0	1.75
6	33	Female	31.6	31.6	30.8	30.8	1.67
7	41	Female	29.0	28.7	28.3	27.9	1.65
8	50	Male	30.6	30.9	31.2	31.2	1.8
9	28	Female	30.8	30.8	30.4	30.1	1.72
10	34	Male	31.6	31.3	31.3	31.6	1.76
11	24	Male	32.9	32.6	32.2	32.6	1.69
12	46	Male	36.4	36.8	36.4	36.1	1.69
13	47	Female	25.4	25.7	25.7	25.7	1.82
AVG	37.5		31.7	31.7	31.5	31.4	1.7
STDEV	9.9		2.8	2.9	2.9	2.8	0.051

emphasizing the importance of double blinded-randomized clinical study in terms of scientific methodology.

We speculate that the combination of the 4 plants in Weighlevel may cause weight loss, in part, due to an increase thermogenesis in brown adipocytes. We measured thermogenesis in male Sprague-Dawley rats [14]. This system is generally accepted as a model for fat depletion (”fat burning”).

The amines of *Alchemilla vulgaris* L. are mainly the tannins reported to increase the metabolic rate in cold environments [11] and the flavonoids reported to regulate digestive enzymes and to have cardioprotective effects [15]. Beside metabolic stimulation [12], olive leaves-extracts have been shown to inhibit intestinal glucose absorption and, thereby, a hypoglycaemic effect was reported together with hypotensive and hypolipidemic properties [16-18]. Olive leaves are thus known to reduce fat load and circulatory fat

levels. Wild mint has been reported to relax the stomach and increase gastric emptying and the passage of food throughout the digestive system [19]. Cumin also has been reported to improve glucose utilization, reduce raised blood sugar and promote digestion by stimulating gastrointestinal mucosa and pancreatic digestive enzymes [20, 21].

REFERENCES

[1] Halpern A, Mancini MC. Treatment of obesity: an update on anti-obesity medications. Obese Rev 2003; 4: 25.

[2] Sena I (Avicenna). Al Qanun Fi al Teb. Book one (Arabic). Lebanon: Dar Alfiker, Bairut 1994.

[3] Razi A (Rhazes). Al Hawi Fi al Teb. Book six (Arabic). Lebanon: Dar Ihiaa Al turaath Al islami: Beirut 2002.

[4] Saad B, Azaizeh, H, Said, O. Tradition and perspectives of Arab herbal medicine: a review. Evid Based Complement Alternat Med 2005; 2: 475-79.

[5] Azaizeh H, Saad B, Khalil KH, Said O. The status of traditional Arab medicine and medicinal herbs of the middle eastern region: review. Evid Based Complement Alternat Med 2006; 3: 229-35

[6] Saad B, Azaizeh H, Abu Hijleh G, Said O. Safety of traditional Arab herbal medicine: a review. Evid Based Complement Alternat Med 2006; 3: 433-39.

[7] The Complete German Commission E Monographs; Integrative Medicine 1999.

[8] Alturkmani IR. Almaatammad Fi Aladwiya. Dar-Al-Kutub Alarabiya, Cairo, Egypt 1930; pp. 319, 432 and 525.

[9] Said O, Khalil, KH, Azaizeh, H, Fulder, S. Ethnopharmacolical survey of the medical herbs in israel, the golan heights and the west bank. J Ethnopharmacol 2002; 83: 251.

[10] Pinelli P. Quali-quantitative analysis of antioxidant activity of different polyphenolic extracts from *Olea europea* L. L. leaves. J Commod Sci 2000; 39: 71.

[11] Borodin IUI, Seliatitskaia VG, Obukhova LA, Pal`chikova NA, Odintsov SV, Kukushkina TA. Effect of polyphenol fraction of *Alchemilla vulgaris L*. on the morphofunctional state of the thyroid in rats exposed to cold. Biull Eksp Biol Med 1999; 127: 697.

[12] Al-Qarawi AA, Al-Damegh MA, El-Mougy SA. Effect of freeze dried extract of *Olea europea* on the pituitary-thyroid axis. Phytother Res 2002; 16: 286.

[13] May B, Kohler S, Schneider B. Efficacy and tolerability of a fixed combination Peppermint oil and caraway oil in patients suffering from functional dyspepsia. Aliment Pharmacol Ther 2000; 14:1671.

[14] Said O, Saad B, Fulder S, Khalil K, Kassis E. Weight loss in animals and humans treated with 'Weighlevel', a combination of four medicinal plants used in traditional arabic and islamic medicine. Evid Based Complement Altern Med 2008; 5: 421-8.

[15] Jonadet M, Meunier MT, Villie F, Bastide JP, Lamaison JL. Flavonoids extracted from *Ribes nigrum L*. and *Alchemilla vulgaris* LL. *In vitro* inhibitory activities on elastase, trypsin and chemotrypsin. 2. Angioprotective activities *in vivo*. J Pharmacol 1986; 17: 21.

[16] Fehri B, Aiache JM, Memmi A, Korbi S, Yacoubi MT, Mrad S, Lamaison JL. Hypotension, hypoglycaemia and hypouricemia recorded after repeated administration of aqueous leaf extract of *Olea europea L*. J Pharm Belg 1994; 49: 101.

[17] Gonzalez M, Zarzuelo A, Gamaz MJ, Utrilla MP, Jimenez J, Osuna I. Hypoglycemic activity of olive leaf. Planta Med 1992; 58: 513.

[18] Said O, Fulder S, Khalil K, Azaizeh H, Kassis E, Saad B. Maintaining a physiological blood glucose level with the help of "Glucolevel", a combination of four anti-diabetes plants used in the traditional Arab herbal medicine. Evid Based Complement Alternat Med 2008; 5(4): 421-8.

[19] Spirling LI, Daniels IR. Botanical perspectives on health peppermint: more than just an after-dinner mint. J R Soc Health 2001; 121: 62.

[20] Platel K, Srinivasan K. Influence of spices and their active principles on pancreatic digestive enzymes in albino rats. Nahrung 2000; 44: 42.

[21] Roman-Ramos R, Flores-Saenz JL, Alarcon-Aguilar FJ. Anti-hyperglycemic effect of some edible plants. J Ethnopharmacol 1995; 48: 25.

Received: October 14, 2009 Revised: October 28, 2009 Accepted: October 29, 2009