In the name of GOD

Effects of Komouni Formulation With a Low-Calorie Diet on Cardiometabolic Risk Factors in Overweight and Obese Women: A Triple-Blinded Randomized Clinical Trial

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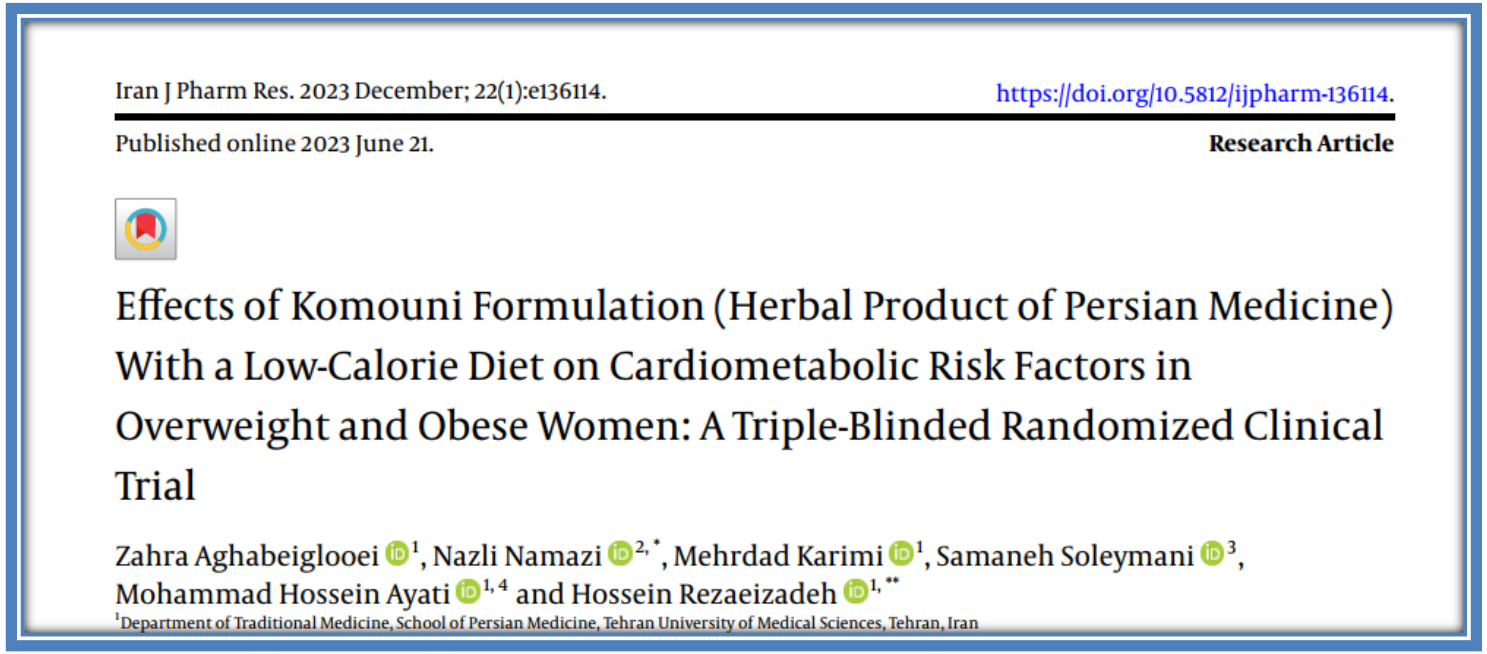
Journal Club



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Published online 2023 June 21. **Research Article**

Effects of Komouni Formulation (Herbal Product of Persian Medicine) With a Low-Calorie Diet on Cardiometabolic Risk Factors in Overweight and Obese Women: A Triple-Blinded Randomized Clinical Trial

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Abstract

- Komouni formulation (KF) is a compound medicine
  - Groups
  - KF or placebo for 8 weeks
    - calorie-restricted diet
    - with 2 g/day (500 mg 30 minutes before breakfast, 1000 mg 30 minutes before lunch, and 500 mg 30 minutes before dinner)

Abstract

- Aim: the effects of KF on anthropometric indices and metabolic parameters in overweight and obese women.
- Population study
  - 70 overweight or obese women aged 20 - 40 years, with a body mass index (BMI) of 25 - 34.9 kg/m2

Abstract

- Assessment : at baseline, after the intervention
  - Anthropometric indices
  - Food intake
  - Biochemical parameters
  - ؟physical activity

Introduction: Background

- Economic burden
- This metabolic disorder is one of the most important risk factors for several chronic disease
  - (diabetes, hyperlipidemia, cardiovascular diseases, fatty liver, and some types of cancer)
- It can increase susceptibility to infections
  - including coronavirus disease 2019 (COVID-19)
- Treatments for obesity in conventional medicine include lifestyle modification (exercise, diet, and behavioral therapy), drug therapy, and surgery with side effects

Introduction: Background

- KF
  - Black caraway (*Bunium persicum* Boiss.)
  - Anise (*Pimpinella anisum* L.)
  - Fennel (*Foeniculum vulgare* Miller)
  - Ajwain (*Trachyspemum ammi .L)*
- *According to the current evidence, the components:*
  - *antioxidant, hypoglycemic, antiatherosclerosis, antidiabetic, appetite suppressant, and anti-obesity activities*

Method: drug preparation

- The formula and placebo capsules were prepared by Tooba Green Gold Company (Tehran, Iran)
- 50% hydroethanolic extracts were prepared by repeated maceration method and then freeze-dried.
- The volume of the resultant lyophilized powder was adjusted with pharmaceutical-grade starch (as a filler)
- Accordingly, each 500 mg capsule contained extracts of 3 gr of fennel, 3 gr of anise, 2 gr of black caraway, 2 gr of ajwain.

Method: drug preparation

- The dose used in this study was consistent with the dose suggested in a valid PM textbook, Qarabadin Salehi.
- The formula mentioned in Qarabadin Salehi includes some components, namely Carum carvi (caraway), Pimpinella anisum (anise), Foeniculum vulgare (fennel), and Trachyspermum ammi (ajwain).

- It should be noted that in reliable PM sources, including the book Makhzan Al-Advieh, Bunium persicum (black caraway) has been introduced as an alternative to caraway due to their similar properties

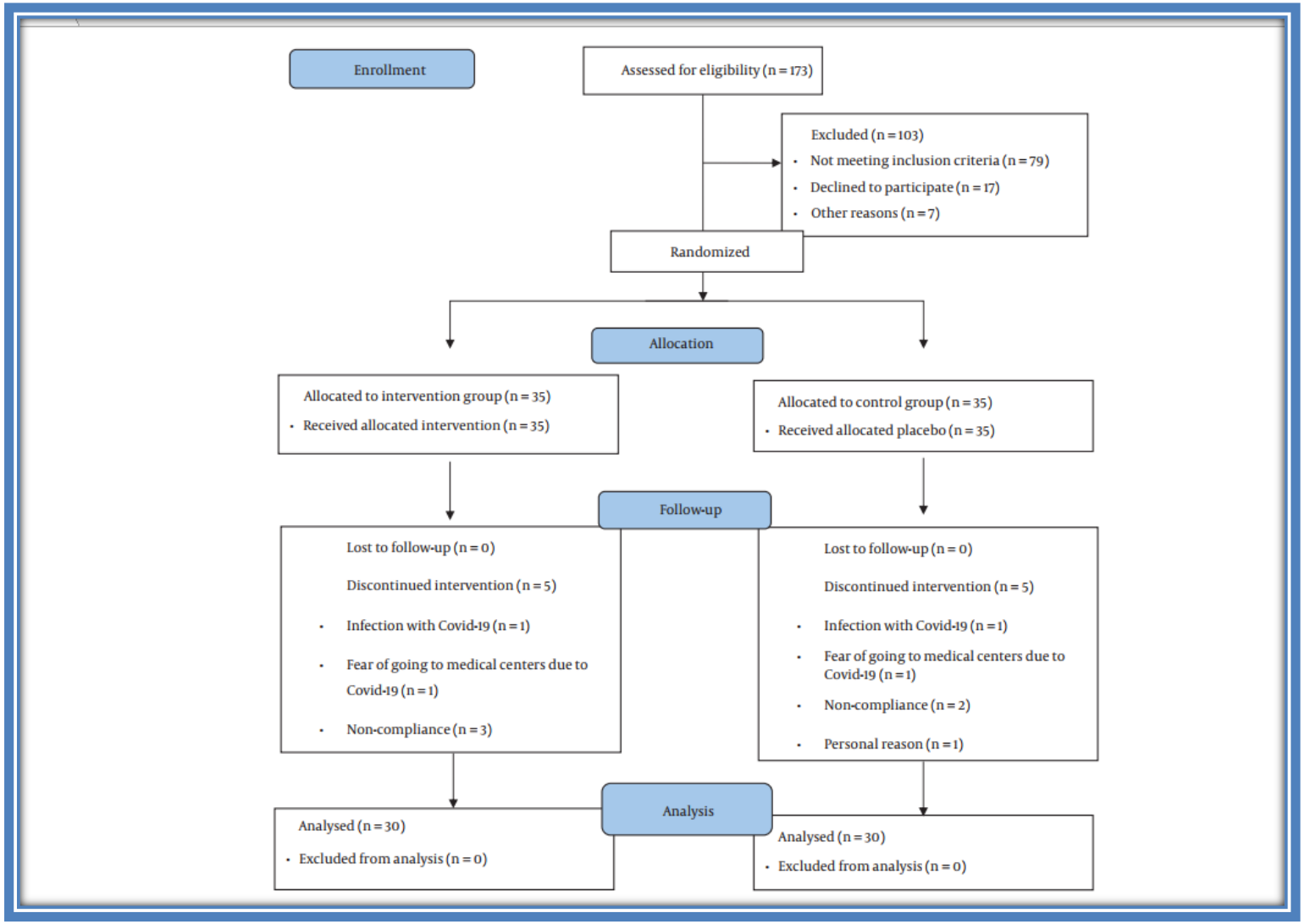
Method: Drug Standardization

- Based on total phenolic and flavonoid content
  - Spectrophotometry to calculate total phenolic content.
  - Colorimetric analysis was used to calculate the total flavonoid content
  - gallic acid and quercetin standards

Method: Participants

- Recruitment posters were put up in the clinics of TUMS and on social networks.
- Volunteers (n = 94) were invited to Ahmadiye Clinic (i.e., a specialized traditional medicine treatment center) for interviews from July to September 2021.

study flowchart



Method: blindness, allocation, concealment

- The capsules were placed in completely similar opaque cans.
- They were encoded by a coinvestigator who was not involved in the study based on the randomized allocation list.
- To achieve **concealment**, the bottled KF and placebo samples were coded by a person who was not involved in the trial.
- The participants were divided into two groups using a random **allocation** list generated by R4.0.2 software.
- The researchers, participants, and a statistician were completely blind to group allocations

Method: Inclusion and Exclusion Criteria

- Inclusion: women aged 20 - 40 or 40 - 50 years with normal mammography and (BMI) of 25 - 34.9 kg/m2

Method: Inclusion and Exclusion Criteria

- Exclusion
- History of cardiovascular, hepatic, renal thyroid or pancreatic diseases, DM, HTN, excessive menstrual bleeding, any type of malignancy, allergies, hormonal disorder, recent or active infectious diseases, pregnancy, lactation, or postmenopause
- Excessive use of decoctions and herbal medicines, smoking or alcohol consumption, a family history of breast or endometrial cancer in first-degree relatives,
- Continuous use of acetaminophen (paracetamol), anticoagulants, or antiplateletdrugs, such as aspirin, warfarin, and heparin
- Following a weight loss diet or having consumed weight loss medications in the past 6 months

Method: study design : baseline

- Written informed consent
- Baseline: questionnaire for general information, including
  - name, age, education, occupation, family history of obesity, history of previous diseases, and used medications: by the researcher
- Observing the principles of medical ethics and the fact that patients were not to be deprived of conventional treatments, an individualized weight loss diet was designed for all the volunteers by a nutritionist

Method: diet design

- Individual diet: The amounts of dietary calories were calculated using the Mifflin equation for all the participants. Based on the personal characteristics and dietary habits of each participant

50%, 20%, and 30% carbohydrate, protein, and fat, respectively

- Total energy expenditure was estimated by considering the coefficient of physical activity and a 10% thermic effect of food

- Since all the participants were overweight or obese, 500 kcal was deducted from the total calculated calories.

Method: grouping

- Intervention group received 2000 mg of KF daily for 8 w
  - (1cap (500 mg) 30 minutes before breakfast, 2 cap (1000 mg) 30 minutes before lunch,1 cap (500 mg) 30 minutes before dinner

- The placebo group received the same amount of oral Avicel

Method: grouping

- Half of the medicines (two 60-capsule containers) were given to the participants at the beginning of the study, and the other half was delivered on the second visit.
- For **compliance assessment**, the participants were asked to deliver their capsule containers (full or empty) to the researcher on the 2nd and 3rd visits

The participants were excluded from the study if less than 95% of the drug was consumed.

- Phone calls were made 1/w to ↓ the risk of **drop-outs**, ensure the correct use of drugs, and obtain information about drug side effects

Method: assessment

- 8 weeks
- 3 face-to-face visits: 0 , 4w, 8w
  - researcher assessed
    - food intake using a 24-hour food recall questionnaire(2 working days and 1 weekend day).
    - anthropometric indices
- 0, 8w
  - Biochemical indicators using blood tests (after 12 hours of fasting) and
  - Physical activity levels usiNg the short form of the International Physical Activity Questionnaire (IPAQ)

Method: Measured Variables

- The amount of food intake was recorded during all visits by the researcher using a 24-hour food recall questionnaire (2 working days and 1 weekend day).

- Nutritionist IV software (version 3.5.2; First Databank Inc., Hearst Corp.,San Bruno, CA, USA), modified to suit Iranian food, was used to measure the amounts of consumed macronutrients and dietary fiber.

Method: Measured Variables

- Anthropometric Measurements:
- Baseline: Height and waist circumference by the researcher
  - Height: without shoes by a Seca stadiometer (Seca, Hamburg, Germany) with an accuracy of 0.5 cm
  - Weight: by Seca scales (Seca, Hamburg, Germany) on all three visits, with an accuracy of 0.1 kg, were fasting, had no shoes on, had minimum clothing, and were asked to wear the same garment in all visits
- In all 3 visits
  - Other Anthropometric Measurements: BMI, Waist circumference (WC), Hip circumference(HC), Wrist circumference, The waist-to-hip ratio (WHR)

Method: Measured Variables

- Anthropometric Measurements
  - Waist circumference: with an inelastic plastic meter in the smallest circumference of the distance between the last rib and the iliac bone with an accuracy of 0.5 cm
  - Hip circumference: with an inelastic plastic meter in the largest HC with an accuracy of 0.5 cm
  - Wrist circumference: with an inelastic plastic meter exclusively from the right side at the junction of the wrist to the forearm on the styloid appendage of the ulnar bone with an accuracy of 0.5 cm

Method: Measured Variables

- Biochemical Evaluation
- 0, 8W
- 8 cc of blood was taken from a vein in the left arm after 12 hours of fasting and while in a sitting position.
- Serum was separated by centrifugation, and the mentioned factors were measured by an enzymatic method immediately after blood sampling.
- using kits with the same LAT number and in the same laboratory.

Method: Measured Variables

- Physical activity
- 0, 8w
- IPAQ was completed by the researcher
- The participants were accordingly divided into three groups, namely sedentary, moderately active, and highly active.

Results: Demographic and Baseline Data

- A total of 70 eligible participants entered the study. Finally, 60 women (intervention = 30; placebo = 30) completed the trial
- no significant difference was observed between the two groups regarding any demographic and baseline variables at the beginning of the study, which indicated optimal randomization
- The mean values of body weight, BMI, and age of the participants were 82.4 ± 10.3 kg, 31.2 ± 2.6 kg/m2, and 35.2 ± 5.4 years

Results

- Inter group : ↓ sig body composition indices
  - Including weight, BMI, WC, and HC, in both groups at the end of the intervention
- Between group
  - the KF group had a more substantial reduction than the placebo group in both weight (-4.8 vs. -3.2 kg; P = 0.0001) and BMI, WC and HC

Results

Table 2. Comparison of Anthropometric Indices at Baseline and After the Intervention

Variables	Komouni Group			Placebo Group			P-value	
	Before	After	P-value [a]	Before	After	P-value [a]	Independent *t*-test	Analysis of covariance [b]
Body composition								
Weight, kg	81.76 ± 11.16	76.97 ± 10.68	0.0001 [c]	83.4 ± 8.47	81.33 ± 8.73	0.0001 [c]	0.0001 [c]	0.001 [c]
Body mass index, kg/m^2	31.29 ± 2.66	29.46 ± 2.62	0.0001 [c]	31.38 ± 2.33	30.59 ± 2.3	0.0001 [c]	0.0001 [c]	0.0001 [c]
Anthropometric indices								
Waist circumference, cm	91.93 ± 8.36	86.65 ± 7.87	0.0001 [c]	92.52 ± 7.49	89.32 ± 7.63	0.0001 [c]	0.004 [c]	0.004 [c]
Hip circumference, cm	111.4 ± 6.6	107.3 ± 6.6	0.0001 [c]	114.4 ± 6.1	111.6 ± 6.8	0.0001 [c]	0.047 [c]	
Waist-to-hip ratio	0.83 ± 0.06	0.81 ± 0.06	0.0001 [c]	0.81 ± 0.05	0.8 ± 0.05	0.013 [c]	0.07	0.130

Results

- Inter group
  - TG, HDL: ↓ significantly in both groups, compared to the baseline ($P < 0.05$)
- Between group
  - The changes were not significant between the two groups

Results

The two groups differed significantly in terms of FBS (-5.6 vs.0.33; P = 0.025), LDL (-11.7 vs. 6.7; P= 0.0001), LDL-to-HDL ratio (-0.09 vs. 0.26; P = 0.007), and cholesterol-to-HDL ratio (-0.20 vs. 0.22; P = 0.022) at the end of the intervention

- No changes in LFT

Results

- Since both groups adhered to the diet throughout the trial, energy intake decreased significantly in both groups ($P < 0.05$) (Table 3).
- Furthermore, the overall effect of the intervention on calories ($P = 0.0004$) was statistically significant.
- Accordingly, in the eighth week of the study, the KF group received an average of 195 kcal less than the placebo group
- The recommended and consumed calories and macronutrients were compared to evaluate adherence to the diet. there was a slight difference

Results

- After the adjustment of energy, dietary intake, baseline values, cholesterol, HDL, and LDL:
  - some variables, including weight, WC, HC, and BMI, reduced significantly in the KF group compared to the placebo group after the intervention ($P < 0.05$)

Results

Table 3. Comparison of Biochemical Parameters and Dietary Intake at Baseline and After the Intervention

Variables	Komouni Group			Placebo Group			P-Value
	Before	After	P-Value	Before	After	P-Value	
Lipid and atherogenic profile							
Cholesterol, mg/dL	379.63 ± 358.73	232.01 ± 218.28	0.0001 [a, b]	332.53 ± 354.69	237.59 ± 240.87	0.0001 [a, b]	0.652 [c]
Triglyceride, mg/dL	137.93 ± 64.63	140.77 ± 67.96	0.707 [b]	138.13 ± 70.05	143.23 ± 58.89	0.0001 [a, b]	0.84 [c]
HDL, mg/dL	40.9 ± 6.5	37.93 ± 6.48	0.011 [a, b]	39.3 ± 8.62	38.53 ± 8.85	0.0001 [a, b]	0.123 [c]
LDL, mg/dL	3.09 ± 0.89	3 ± 0.71	0.003 [a, b]	3.09 ± 1.05	3.35 ± 1.09	0.0001 [a, b]	0.0001 [a, c]
LDL-to-HDL ratio	3.09 ± 0.89	3 ± 0.71	0.355 [b]	3.09 ± 1.05	3.35 ± 1.09	0.003 [a, b]	0.007 [a, c]
Cholesterol-to-HDL ratio	4.95 ± 1.14	4.75 ± 0.92	0.144 [b]	4.98 ± 1.4	5.2 ± 1.44	0.072 [b]	0.022 [a, c]
Fasting blood sugar, mg/dL	95.8 ± 12.7	90.2 ± 8.4	0.009 [a, b]	91.7 ± 5.0	91.4 ± 7.7	0.770 [a, b]	0.026 [a, c]
Aspartate aminotransferase, U/L	20.2 ± 9.0	17.6 ± 5.6	0.142 [a, b]	20.6 ± 9.9	18.4 ± 8.5	0.297 [a, b]	0.861 [c]
Alanine transaminase, U/L	26.7 ± 20.7	26.3 ± 10.9	0.896 [a, b]	26.5 ± 20.9	26.8 ± 11.1	0.954 [a, b]	0.896 [c]
Energy and macronutrients consumption							
Energy, kcal/d	2705.3 ± 180.17	1770.1 ± 212.9	0.0001 [a, b]	2620.6 ± 207.79	1908.27 ± 131.02	0.542 [b]	0.0001 [a, c]
Carbohydrates, g/d	363.22 ± 73.09	221.6 ± 52.82	0.0001 [a, b]	359.23 ± 60.31	249.86 ± 61.63	0.928 [b]	0.723 [c]
Protein, g/d	105.76 ± 23.77	71.22 ± 16.4	0.0001 [a, b]	100.67 ± 19.05	82.6 ± 16.59	0.666 [b]	0.011 [a, c]
Total fat, g/d	94.1 ± 24.3	59.54 ± 17.54	0.0001 [a, b]	91.01 ± 24.49	61.75 ± 22.1	0.592 [b]	0.529 [c]
Micronutrients consumption							
Fiber	20.37 ± 7.78	15.24 ± 5.9	0.009 [a, b]	22.55 ± 7.24	16.52 ± 5.58	0.332 [b]	0.725 [c]
Iron	27.01 ± 5.16	18.21 ± 4.08	0.0001 [a, b]	26.95 ± 5.73	20.51 ± 4.53	0.415 [b]	0.145 [c]
Calcium	932.25 ± 225.16	763 ± 330.42	0.038 [a, b]	900.51 ± 200.8	802.52 ± 294.31	0.337 [b]	0.50 [c]
Cobalamin	20.37 ± 38.39	16.56 ± 33.31	0.668 [b]	15.58 ± 39.48	17.59 ± 33.18	0.450 [b]	0.664 [c]
Vitamin A	4257.86 ± 4893.51	3556.07 ± 2748.49	0.472 [b]	4325.68 ± 4917.56	3560.99 ± 2771.44	0.977 [b]	0.965 [c]
Vitamin D	0.86 ± 0.78	0.58 ± 0.69	0.114 [b]	1.02 ± 0.7	0.71 ± 0.89	0.982 [b]	0.944 [c]

Results

Table 4. Comparison of the Recommended and Consumed Calories and Macronutrients to Evaluate Adherence to Diet [a]

Variables	4th Week		8th Week	
	Komouni Group	Placebo Group	Komouni Group	Placebo Group
Energy, kcal/day				
Recommended	1779.1 ± 219.9a	1830.3 ± 179.3	1779.1 ± 219.9	1830.3 ± 179.3
Consumed	1742 ± 209.4	1908.2 ± 131.0	1698.6 ± 217.5	1866.4 ± 163.1
P-value [b]	0.458	0.057	0.183	0.435
Protein, % of total energy				
Recommended	20 ± 0	20 ± 0	20 ± 0	20 ± 0
Consumed	19.0 ± 7.5	16.0 ± 2.5	16.8 ± 4.0	18.5 ± 6.1
P-value	0.506	0.000	0.000	0.204
Carbohydrate, % of total energy				
Recommended	50 ± 0	50 ± 0	50 ± 0	50 ± 0
Consumed	50.9 ± 10.8	53.5 ± 10.7	51.6 ± 8.7	52.3 ± 11.2
P-value	0.628	0.079	0.307	0.259
Total fat, % of total energy				
Recommended	30 ± 0	30 ± 0	30 ± 0	30 ± 0
Consumed	30.1 ± 10.2	30.1 ± 9.7	31.3 ± 8.3	29.3 ± 10.4
P-value	0.930	0.926	0.391	0.716

Conclusion

- The results indicated that daily consumption of 2000 mg of KF, along with a calorie-restricted diet, for 8 weeks can significantly reduce
- Weight
- WC
- HC
- FBS
- LDL
- reduce cardiometabolic risk factors in overweight and obese women

Discussion

- Caraway studies
  - anti-obesity effects of caraway in obese women(weight, BMI, fat percentage, and WHR)
  - But not LDL reduction
- Fennel
  - aromatherapy with fennel reduces appetite in obese individuals

Discussion

- 10 gr of ajwain decreases LDL and increases HDL

Black caraway

- Antioxidant
- Hypoglycemic
- weight-reducing
- Antihypertensive
- anti dyslipidemic properties
- Possible mechanisms include the
  - ↓ of ghrelin (appetite stimulating hormone)
  - ↓ of production of visceral fat and,
  - thereby lowering pro-inflammatory cytokines produced in these tissues (by carvacrol)

Anise

- Antioxidant
- antidiabetic
- anti-inflammatory
- anti-atherosclerotic,
- anti-obesity
- antihypertensive
- lipid-lowering
  possible mechanisms of these properties is
- ↓ of triglyceride, saturated fats, and cholesterol

Fennel

- Trans-anethole, a substance extracted from fennel's essential oil, is structurally similar to catecholamines and acts similarly to amphetamines in controlling appetite.
- It is one of the possible mechanisms that fennel causes weight loss

ajwain

- The lipid-lowering effect of ajwain is proposed to be due to improved lipoprotein catabolism, inhibition of HMG-CoA reductase, and inhibition of lysosomal lipid hydrolytic enzymes secreted by the **liver**

Discussion

- four abovementioned medicinal plants and possible mechanisms,
- it is predicted that this formula might help weight management in obese and overweight individuals via the synergistic effects of mechanisms

Discussion

- These effects include appetite suppression via
- ↓ ghrelin,
- ↑in conjugated linoleic acid (both suppressing appetite and lowering blood lipids)
- and trans-Anethole improvement in lipoprotein catabolism, inhibition of HMG-CoA reductase, and inhibition of lysosomal lipid hydrolytic enzymes.

Discussion

- Additionally, the herbs used in this formula have a hot-dry temperament (Mizaj) based on PM

The possible PM-based mechanism includes the drying action of the comprising herbs, which

- dissolves excessive moisture and phlegmatic substances in the gastrointestinal tract and other body parts, thereby reducing body fat.

Via a reinforcing action on digestion and the gastrointestinal system, they also improve body metabolism and reduce the production of phlegmatic substances and fat.

This formula may eliminate two of the most important causes of obesity, namely low metabolism and poor digestion

Study limitation

- difference in the lifestyle of the participants.
- This study evaluated these differences to some extent by using a physical activity questionnaire and a food diary.
- However, according to PM, consuming similar calories is not necessarily enough because each food's hot or cold nature can induce different effects in individuals

Pimpinella anisum

انیسون: Pimpinella anisum

تریایت. قبض. عطریت. تقویت اعضا. محلل ریاح و بلاغم غلیظ

۱- حوزه گوارش: نفخ سوهاضمه. ریفلاکس ضعف فم معده صداع مشارکتی با معده

۲- حوزه زنان: الیگومنوره. PCO. شیرافزا. فیتواستروژن. گرگرفتگی. انیسون باعث کاهش FSH و افزایش ضخامت آندومتر نیز میشود.کاهش علائم PMS. سیلان رحم. واژنیت گاردنلایی. حبس طمث(مدر حیض). جلوگیری از استئوپورز در یائسگی

۳- حوزه ریوی: آسم (خصوصا در همراهی با شیرین بیان)

۴- حوزه دماغ: نزله، سینوزیت. صداع. مالیخولیا. کابوس. افزایش سروتونین. تقویت حافظه. مقوی دماغ. پارکینسون

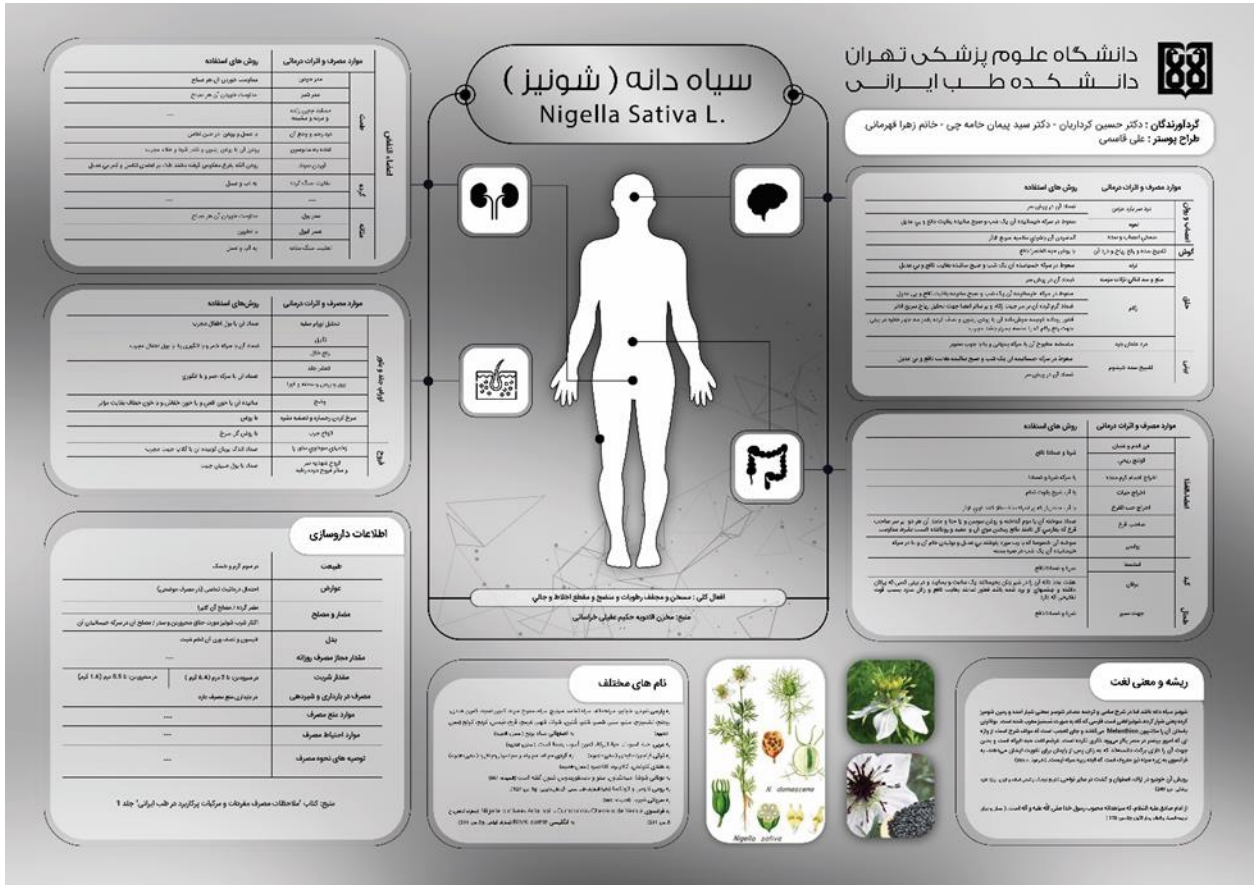
۵- حوزه کبدی: شدیدالنفع برای کبد. رفع سده. مقوی روح کبد بافت کبد. نضج فضولات کبدی

۶- حوزه کلیوی: مفتت حصاه

کانتراندیکاسیونهای انیسون:

- ✓ بارداری
- ✓ سابقه کانسربرست استروژن مثبت
- ✓ مصرف کنندگان وارفارین
- ✓ آلرژی به آنتول
- ✓ آندومتریوز
- ✓ هایپرپلازی آندومتر(احتیاط)
- ✓ بالا بودن پرولاکتین

DR SOMAYE ZAKERI


دانشگاه علوم پزشکی تهران
دانشکده طب ایرانی
سیاه دانه (شونیز)
Nigella Sativa L.
گردآورندگان : دکتر حسین کرداریان - دکتر سید پیمان خامه چی - خانم زهرا قهرمانی
طراح پوستر : علی قاسمی
موارد مصرف و اثرات درمانی
روش های استفاده
اطلاعات داروسازی
ریشه و معنی لغت
نام های مختلف
Nigella sativa
N. damascena

Blindness

- Blindness (masking): preventing participants, the researchers, or both from knowing which treatment or intervention is being administered. This is done to minimize bias that may arise due to expectations or beliefs about the treatment effect.
- Single-blind study: Participants are unaware of which treatment they are receiving, but the researchers know.
- Double-blind study: Both participants and researchers are unaware of the treatment allocation.
- Triple-blind study: In addition to participants and researchers, data analysts also do not know the treatment allocation.
- Trained interviewer : collection of data

Allocation

- Allocation refers to the process of assigning participants to different treatment groups in an RCT. It involves randomly allocating individuals to either the experimental group or the control group (receiving a placebo or standard treatment).
- Random allocation helps ensure that each group is comparable at the start of the study, reducing the likelihood of confounding variables affecting the results.

Concealment

- Concealment refers to the practice of keeping the treatment allocation hidden or concealed from both participants and researchers until the point of assignment.
- It prevents potential bias that could arise if participants or researchers are aware of the group to which individuals are being allocated.
- Concealment is achieved through methods like central randomization, sequentially numbered, opaque, sealed envelopes, or an automated web-based randomization system.
- **Allocation concealment is a different concept to blinding**. It means that the person randomising the patient does not know what the next treatment allocation will be. It is important as it prevents selection bias affecting which patients are given which treatment (the bias randomisation is designed to avoid)

Bias

Biases

Selection Bias

When there is ***no RAB***; i.e. no ***R***ight clinical question, no inclusion or exclusion c***R***iteria, no proper ***A***rticles searching, no proper ***A***ppraisal and no ***B***linded independent reviewers.

Publication Bias

Happens when journals and authors only published articles with outcome of interest.
It can be detected through ***funnel plot***.