Research article

The effects of MIND diet and propolis supplementation on metabolic syndrome: A randomized controlled clinical trial☆

Zainab Gholami [a], Mohammad Reza Maracy [b], Zamzam Paknahad [c,*]

[a] School of Nutrition and Food Science, Students' Research Committee, Department of Clinical Nutrition, Isfahan University of Medical Sciences, Isfahan, Iran
[b] Department of Epidemiology and Biostatistics, School of Health, Isfahan University of Medical Sciences, Isfahan, Iran
[c] Department of Clinical Nutrition, Faculty of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran

ABSTRACT

The MIND is a novel eating plan preserves cognitive function. Propolis is a resinous substance that has several biological and medicinal properties. This study examines the effect of the MIND diet and propolis supplementation on MetS indices among metabolic syndrome subjects. This RCT study, was conducted on adults with metabolic syndrome who were referred to the Hazrat Ali Health Center in Isfahan. 84 eligible subjects were divided into 3 groups. Including MIND diet + Propolis supplement, MIND diet + placebo, and control group. The data obtained from the subjects was analyzed in two descriptive and analytic levels. The Shapiro-Wilk test and examination of skewness were conducted to assess the normality of the distribution of quantitative variables. Quantitative variables were reported using either the mean (SD). SPSS Statistics software version 26 was used for statistical analysis of data. In this study the MIND + Propolis group compared to the control group after adjusting variables showed a significant decrease (p-value < 0.05) in weight, BMI, WC, SBP, DBP, and TG by 0.97 times (3%), 0.97 times (3%), 0.98 times (2%), 0.93 times (7%), 0.94 times (6%), and 0.75 times (25%), respectively; this significant change was also observed in FBS (p-value < 0.001) by 0.85 times (15%), and HDL-C (mg/dl) has shown a significant increase (p-value < 0.05) by 1.17 times (17%). MIND group compared to the control group after adjusting variables showed a significant decrease (p-value < 0.05) in BMI, WC, and SBP by 0.98 times (2%), 0.98 times (2%), and 0.95 times (5%), respectively; this significant change (p-value < 0.001) was also observed in DBP, FBS, and TG by 0.92 times (8%), 0.83 times (17%), and 0.71 times (29%), respectively; HDL-C has shown a significant increase (p-value < 0.001) by 1.21 times (21%), and weight has shown a non-significant decrease (p-value = 0.055) by 0.98 times (2%). This study indicated that the MIND diet + Propolis supplement and MIND diet compared to the control group can significantly decrease BMI, WC, SBP, DBP, FBS, TG, and weight (non-significant for the MIND group), and also increase HDL-C.

Abbreviations

MIND	The Mediterranean-DASH Intervention for Neurodegenerative Delay diet
MetS	Metabolic Syndrome
RCT	Randomized Controlled Clinical Trial
BMI	Body Mass Index
WC	Waist Circumference
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
TG	Triglyceride
FBS	Fasting Blood Sugar
HDL-C	High Density Lipoprotein Cholesterol
NCEP	National Cholesterol Education Program
ATP III	Adult Treatment Panel III
DASH	Dietary Approaches to Stop Hypertension
MD	Mediterranean Diet
CAV1	Caveolin 1
CVD	Cardiovascular Disease
HbA1c	Hemoglobin A1c
CRP	C-Reactive Protein
TNF-α:	Tumor Necrosis Factor Alpha
LDL-C:	Low Density Lipoprotein Cholesterol
HOMA IR	Homeostatic Model Assessment for Insulin Resistance
HIV	Human Immunodeficiency Virus
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
GLM	Generalized Linear Model
SAMPL	Statistical Analyses and Methods in the Published Literature
OEA	Oleic Acid Elevates Oleoylethanolamide
MUFA	Monounsaturated Fatty Acids
ATP	Adenosine Triphosphate
ABCA1	ATP-Binding Cassette TransporterA1
PPAR	Peroxisome Proliferator-Activated Receptor
GLUT	Glucose Transporter
PI3K	Phosphatidyl Inositol 3-Kinase
AMPK	Monophosphate-Activated Protein Kinase
AGEs	Advanced Glycation End products
RAGEs	Receptors of Advanced Glycation End products
SD	Standard Deviation
PM	Persian Medicine
CAM	Complementary and Alternative Medicine
RDN	Registered Dietitian Nutritionists

1. Introduction

MetS as a major public health problem is outgrowing the world. Urbanization, excessive energy intake, high obesity prevalence, and decreased physical activity are contributing factors to this trend [1]. Based on NCEP ATP III, three or more of the following indices including: low HDL-C, hypertriglyceridemia, hypertension, central obesity, and high FBS are considered as MetS [1–4]. All subgroups have a marked increase in the frequency of MetS occurrence with age. The prevalence is 19 % in the 20–39 age group and 48 % in the 60-year age group [3]. The prevalence of MetS is generally estimated to be 30.4 %. Findings from multiple studies have indicated that approximately one-third of Iranian adults aged twenty and above have MetS, and the prevalence increases with age [5]. The high rate of obesity among Iranians may be attributed to their eating habits, including consumption of a high-calorie diet and refined carbohydrates [6].

The MIND diet integrates components of the DASH and MD diets to protect cognitive function. According to the first MIND diet study, those who have the highest score showed a lower incidence of cardiovascular disease. MIND diet components include berries, nuts, green leafy vegetables, other vegetables, whole grains, beans, poultry, seafood, olive oil, and wine which are healthy food items. It also includes cheese, butter margarine, red meat, sweets, fast food, and fried foods, which are considered unhealthy food items [7]. The MIND diet emphasizes green leafy vegetables and berries consumption. It also includes cakes and sweets, fast food, fried food, butter, or margarine which aren't observed in the MD or DASH diet [4].

One study showed a significant correlation between the MIND diet and decreasing HDL-C levels and general obesity [4]. CAV1 gene variant rs3807992, a genetic marker that may be used to identify people with an increased risk of MetS can be modified [8]. One study indicated that adherence to the MIND diet was associated with reduced lipid profile and general obesity [9]. No significant correlation was found between MIND and the prevalence of hypertension in the adult population [10]. The MIND diet was generally linked with improvement in blood pressure, glycemic control, and lipid profile [11].

Propolis is a resinous substance that is produced by a combination of buds, and plant secretions with bees' salivary enzymes, it is a compound and sticky substance used in the hive [12,13]. Propolis has several biological and medicinal properties such as immune modulator, anti-tumor, antimicrobial, anti-inflammatory, and antioxidant [14]. Some studies have shown a significant reduction in serum fasting glucose levels, and lipid profiles after consuming propolis supplement [12,13], and also an increase in serum HDL-C [13]. Another study has shown a significant decrease in TG and an increase in HDL-C. However, no significant changes were observed for BMI, weight, total cholesterol and LDL-C [15]. One study demonstrated that propolis may be beneficial in reducing waist circumference [16].

The impact of chronic conditions like MetS in public health is proven. According to the role of the MIND diet and propolis supplementation in correcting MetS indices, and because of limited and contradictory studies on subjects, we decided to study the effects of the MIND diet and propolis supplementation on MetS indicators (lipid profile, blood sugar, blood pressure, waist circumference) in patients with MetS.

2. Materials and methods

The present study is in agreement with the Declaration of Helsinki and its later amendments and has received prior approval from the Medical Ethics Committee of Isfahan University of Medical Sciences, with an ethics code of IR.MUI.RESEARCH.REC.1401.330 with grant no. 3401567. Before enrollment, written and verbal informed consent was obtained from all the participants.

2.1. Study population

In this randomized controlled clinical trial, the population in this study were adults (18–60 years old) who had metabolic syndrome. To diagnose metabolic syndrome based on guidelines NCEP ATP III was performed. Adults with metabolic syndrome who had visited Hazrat Ali Health Center in Isfahan were contacted and the description of the study was explained to them and we asked them to participate in the Study. Eighty-four adults with metabolic syndrome volunteers (thirty-one males and fifty-three females) were selected to participate in this study (4 people dropped out before the start of the study, one person started another diet, and one person was unable to continue the study due to travel, if each participant excluded from the study, we quickly would replace them with another person). The flow diagram of participants throughout the study is shown in Fig. 1.

2.2. Inclusion and exclusion criteria

2.2.1. Inclusion criteria
Adults aged between 18 and 60 years old, with metabolic syndrome (to diagnose metabolic syndrome according to NCEP ATP III), that were referred to Hazrat Ali Health Center in Isfahan were the Inclusion criteria of our study.

2.2.2. Non-entry criteria
Patients who had neurological and psychiatric illnesses including depression, Parkinson's disease, Alzheimer's disease, thyroid disorders, anemia, diabetes, mental disorders, and a history of receiving intensive medical care, experienced a stroke or an ischemic attack within the previous 90 days, with Past medical history of brain damage, HIV and hepatitis C, liver and kidney diseases, and weight changes, within the previous five years received a cancer diagnosis, and patients who were obese and had a BMI greater than 40 didn't enter to our study.

2.2.3. Exclusion criteria of samples
Participants' lack of cooperation throughout different project implementation phases, got on a particular diet, Pregnancy while the study was ongoing, had a disease that prevented them from being interviewed, such as a stroke, memory loss, or another condition, Other chronic illnesses such as severe heart failure, thyroid disease, chronic liver cirrhosis, kidney failure, rheumatoid arthritis, inflammatory bowel disease, weakness, and thinness, and blood clotting after consumption of propolis excluded from our study.

2.3. Study design

This investigation is a parallel RCT. We use the CONSORT checklist as Schulz KF, Altman DG, and Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomized trials [17].

Following a diagnosis of metabolic syndrome, subjects were sequentially chosen for the Hazrat Ali Health Center in Isfahan, we contacted the people who were covered by Hazrat Ali Health Center and if they wanted, and if they met the entry criteria, they were recruited.

We started this study on June 16, 2023.The subjects first were informed of the importance of research and why they must participate in the current study. An informed consent form for the plan was given to eligible individuals.
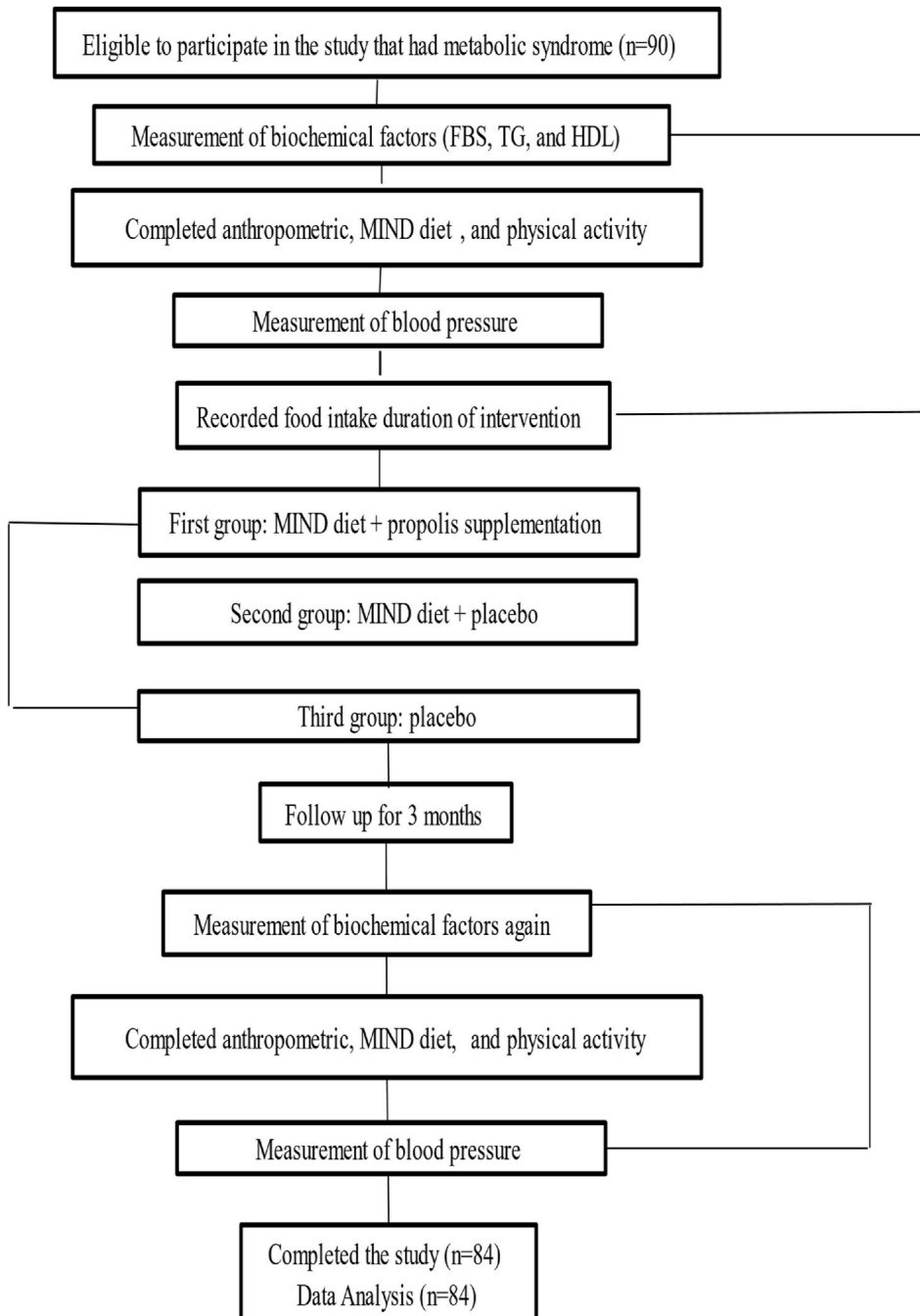
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┌─────────────────────────────────────────────────────────────────┐
│   Eligible to participate in the study that had metabolic syndrome (n=90)   │
└─────────────────────────────────────────────────────────────────┘

    ┌───────────────────────────────────────────────────────┐
    │   Measurement of biochemical factors (FBS, TG, and HDL)   │
    └───────────────────────────────────────────────────────┘

    ┌───────────────────────────────────────────────────────┐
    │   Completed anthropometric, MIND diet , and physical activity   │
    └───────────────────────────────────────────────────────┘

        ┌───────────────────────────────────────┐
        │      Measurement of blood pressure      │
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        ┌───────────────────────────────────────┐
        │   Recorded food intake duration of intervention   │
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        │   First group: MIND diet + propolis supplementation   │
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        ┌───────────────────────────────────────┐
        │      Second group: MIND diet + placebo      │
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        │          Third group: placebo          │
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            ┌───────────────────────────────┐
            │      Follow up for 3 months      │
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        ┌───────────────────────────────────────┐
        │   Measurement of biochemical factors again   │
        └───────────────────────────────────────┘

    ┌───────────────────────────────────────────────────────┐
    │   Completed anthropometric, MIND diet,  and physical activity   │
    └───────────────────────────────────────────────────────┘

        ┌───────────────────────────────────────┐
        │      Measurement of blood pressure      │
        └───────────────────────────────────────┘

            ┌───────────────────────────────┐
            │      Completed the study (n=84)      │
            │        Data Analysis (n=84)        │
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Fig. 1. Flow diagram of participants throughout the study.

A randomized block design was used to assign samples to the intervention and control groups while patients were randomly divided into three groups and placed in blocks of three. Randomization aims to mitigate selection bias, which can only be accomplished if consenting patients are unable to predict or alter a patient's treatment assignment before trial registration. This measure is referred to as 'allocation concealment'.

There were 28 blocks of three with the qualified subjects that were referred to. The first, second, and twenty-eighth blocks contain the first, second, and twenty-eighth eligible subjects, respectively. Codes A, B, and C were taken into consideration for the intervention and control groups (control, MIND diet + Propolis supplement, and MIND diet + placebo). The subjects of each block were determined by a table of random numbers, with treatment A applied if the random number was 1–3, treatment B if it was 4–6, and treatment C if it was 7–9 (random numbers produced by a computer can also be used for this purpose). As a result, the first person in the block was given the treatment code that corresponds to the random number, based on the received random number. The design expert was then assigned random numbers to treatments A, B, and C after this procedure was carried out until 28 blocks were finished. At this point, only the designated experts were familiar with A, B, and C. The A, B, and C codes didn't open until all the subjects had signed up for the study. The Expert does not have a role in grouping people and does not group people out of her taste and purposely the steps are done completely randomly and all patients started the study at the same time to avoid any errors. The design expert is not involved in the assignment of treatment codes in another aspect of the study design.

2.4. Information collection methods

Through interviews and form completion, demographic and health history data, such as age, sex, education level, marital status, medical history, and use of drugs, supplements, and herbal medicines, were gathered. Before and after the intervention, we assessed the subjects' food intake, anthropometric indices, blood pressure, lipid profile, blood sugar, and physical activity.

2.5. Anthropometric assessment

Height, weight, and waist circumference are anthropometric measurements that were taken and recorded by a qualified individual. The weight was measured without shoes, with minimal clothing, by a scale with an accuracy of one hundred grams, and the height was measured without shoes with an accuracy of half a centimeter, in a standing position with the hips and shoulders touching the wall and the head in a horizontal position. The BMI of subjects was calculated by dividing their weight (in kilograms) by the square of their height (in meter^2). Also, the WC was measured as an index of fat distribution, the person wore minimal clothes, and the inflexible meter was placed in the smallest circumference of the circle between the chest and thigh without putting compression on the body with an accuracy of 0.01 cm [18].

2.6. Diagnosis of metabolic syndrome

According to recommendations from the NCEP ATP III, metabolic syndrome was diagnosed [19]. It was deemed metabolic syndrome if at least three of the following criteria were presented. All subjects undergo these examinations in a designated laboratory at the start and finish of the investigation.

a) Equal to more than 150 mg/dL of TG.
b) Less than 40 and 50 mg/dL, respectively, for men's and women's HDL_C levels.
c) Blood pressure readings that are equal to more than 130 mmHg for the systolic and 85 mmHg for the diastolic phases, respectively.
d) Equal to more than 100 mg/dL of FBS.
e) Men's and women's WC are equal by more than 102 and 88 cm, respectively [20,21].

2.7. Blood pressure measurement

Following completion of two-thirds of the questionnaire and following approximately 40 min of rest, SBP and DBP were measured with a calibrated sphygmomanometer in a sedentary position three times at 5-min intervals. The blood pressure was calculated as the mean of the second and third numbers [20].

2.8. Measurement of biochemical factors

Blood samples were taken in the Laboratory of Hazrat Ali Health Center after 12 h of fasting to measure the levels of FBS, TG, and HDL-C. Twenty-four hours before the blood sample, we asked the participants to refrain from engaging in strenuous exercise, consuming alcohol, or consuming caffeinated beverages. An auto-analyzer was used to carry out each laboratory test according to a set protocol.

2.9. Dietary assessment

A three-day food record was used to ascertain the subjects' dietary intake. Each participant kept a detailed food record for two workdays and one day off in each month. The 10th, 18th, 25th, 38th, 50th, 55th, 69th, 73rd, and 90th days in during of our study. Next,

using Nutritionist IV software version 3.5.2, the dietary data was extracted. Additionally, the mean quantity of energy consumed in each month as well as the macro- and micronutrient intake were noted [22].

2.10. Assessment of physical activity

Every person's daily physical activity was noted and converted into a metabolic equivalent [23]. We asked people to continue their previous physical activity routines without offering any advice regarding the quantity of physical activity.

2.11. Intervention

The duration of our study was from the July 26, 2023 to the October 26, 2023. The MIND diet and a placebo were given to one group, while the MIND diet and a propolis supplement were given to the other. These two groups were referred to as the intervention groups. The control group was given a microcrystalline cellulose placebo along with customary dietary advice. We use microcrystalline cellulose as placebo because it is a white, neutral, non-reactive, insoluble, free-flowing versatile excipient [24]. The supplementation and the placebo were prepared in the Pharmacology Department of Mashhad University of Medical Sciences, and neither the participants nor the researchers knew what they received until the end of the study. Two intervention groups were given the regular food recommendations as well as the control group, and any calorie restrictions weren't taken into account for all three groups. It was different from the person who delivered the intervention to prevent bias in the data collection process.

After classification, the recruited subjects worked with the researchers for 12 weeks. Patients were required to record at least three dietary intakes in each month (two days on weekdays and one day on the weekends) and to contact us once a week by phone and in person (in the last week) to assess compliance. A minimum of 70 % of the subjects' dietary records must have been completed (i.e., 2 out of 3 records) were deemed qualified, and the subjects were taught daily self-monitoring techniques (to persuade adherence to the recommended diet and nutritional guidelines). To increase patients' motivation, motivational tactics like newsletters and website activities were used.

For each of the three groups separately, the first individual visit included a brief discussion of diet basics, suggestions for general dietary advice, and the administration of supplements.

2.11.1. MIND diet group

Instructions on what foods to include in the diet as well as the methods for supplying these foods were included in the counseling plan for the intervention diet group.

The MIND diet was extracted from Morris. Participants in the MIND diet group were given instructions on how to change their diet, emphasizing natural and plant-based foods, and consuming green leafy vegetables and berries, fish, whole grains, olive oil, and nuts with restricted consumption of high saturated fat and animal food. Iranians are not allowed to drink alcohol, as per Islamic culture and customs. Therefore, we encouraged our patients to use grapes, grape juice, and raisins instead of alcohol [25]. People were required to visit the relevant center three times (on days 7, 46, and 81 of the study), during which time they received the MIND diet specifically seven days a week and received counseling for at least 30 min. Each meeting lasted at least 15 min to check on participants' compliance with the diet and provide counseling. Regular dietary advice was also used, including written and verbal general information about healthy food selections from the healthy food plate. The following are the foundational tenets of the food recommendations that were introduced to all participants.

a) Eat slowly, taking your time to thoroughly and happily chew each bite.
b) Use grilled, steamed, and boiled foods as alternatives to fried.
c) Before cooking your chicken or meat, trim off any extra fat and skin.
d) Use whole-meal bread and mixed rice and oat as opposed to simple rice and pasta.
e) Please don't remove any meals.
f) Frequently consume small meals.
g) Reduce your consumption of fatty and sugary foods.

This combination is more in line with Iranian dietary habits [22].
This group also got a placebo.
We taught participants how to adherence diet. Weekly assessments of the MIND diet score questionnaire and the food record were used to gauge compliance with the dietary intervention. Individuals who fulfilled the requirements for 80 percent or more of their meals and snacks were deemed to be following the MIND diet [25].

2.11.2. Components of the MIND diet

Butter and margarine, red meat, sweets, cheese, fast food, and fried foods are among the five unhealthy food groups. The healthy food groups are nuts, green leafy vegetables, other vegetables, beans, berries, poultry, seafood, whole grains, and olive oil. The MIND diet's overall score, which can be up to 14 points, is determined by adding the points, which are based on 0, 0.5, or 1.

We listed the frequency of food consumption for the other dietary score components. If olive oil was the subjects' main edible, it received a score of 1, and if not, it received a score of 0 [7].

	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			Close-out
TIMEPOINT	**-3wk**	**0 wk**	**0 wk**	**6 wk**	**12 wk**	**12 wk**
ENROLMENT:						
Eligibility screen	*					
Informed consent	*					
Allocation		*				
INTERVENTIONS:						
MIND diet + placebo			●———————————●			
MIND diet + propolis supplementation			●———————————●			
placebo			●———————————●			
ASSESSMENTS:						
general characteristic		*				
biochemical assay		*				*
body mass index		*				*
Waist circumference		*				*
Blood pressure		*				*
Dietary intake		*				*
Physical activity		*				*
Possible side effect			*	*	*	
Participant compliance			*	*	*	

Fig. 2. The SPIRIT figure outlines the enrollment, interventions, and assessments schedule according to the Standard Protocol Items: Recommendations for Interventional Trials.

2.11.3. MIND diet + propolis group

The typical food recommendations for the first group were communicated to the MIND diet + propolis group. The propolis supplement was made at Mashhad University of Medical Sciences' Department of Pharmacology. (450 mg twice daily, before lunch and dinner) were given to them [26] for 12 weeks. Propolis dosage is determined by choosing a phase II trial (Zhao et al., 2016) [27].

2.11.4. Compliance of the subjects

The initiation, midpoint, and end of the study all referred to subjects. Additionally, weekly phone calls and texts were used to monitor the diet and supplement's regular consumption schedule. Furthermore, individuals were asked to indicate their daily consumption by checking the corresponding table. In addition, the amount of unused supplement packaging that the patients returned was calculated after the study.

2.11.5. Control group

Regular dietary advice was also used, including written and verbal general information about healthy food selections from the healthy food plate. The following are the foundational tenets of the food recommendations that were introduced to all participants.

a) Eat slowly, taking your time to thoroughly and happily chew each bite.
b) Use grilled, steamed, and boiled foods as alternatives to fried.
c) Before cooking your chicken or meat, trim off any extra fat and skin.
d) Use whole-meal bread and mixed rice and oats as opposed to simple rice and pasta.
e) Please don't remove any meals.
f) Frequently consume small meals.
g) Reduce your consumption of fatty and sugary foods.

This combination is more in line with Iranian dietary habits [22].

This group also got a placebo in the form of microcrystalline cellulose; the supplementation and the placebo were prepared in the Pharmacology Department of Mashhad University of Medical Sciences, and neither the participants nor the researchers awarded them until the study was over.

2.12. Study registration

The Iranian Registry of Clinical Trials (www.irct.ir), which has the registration reference IRCT20230105057054N1, approved the protocol for the current study on March 28, 2023. The SPIRIT statement was adhered to in the design and reporting of the study. Fig. 2 displays the SPIRIT flow diagram, which describes the timetable for recruitment, interventions, and assessments.

2.13. Sample size and sampling method

$$n_1 = \left(1 + \sqrt{g-1}\right) \frac{(z_1 + z_1)^2\ s^2}{d^2} + \frac{z_1^2\ \sqrt{g-1}}{2\left(1 + \sqrt{g-1}\right)}$$

Table 1
Demographic information of study participants at baseline (n = 84).

Variable		Before			
		Mind- propolis	MIND- placebo	Placebo	p-value
Age; mean (SD)	**Year**	52.9 (6.5)	51.3 (5.3)	53.0 (5.40)	0.484
Physical Activity; mean (SD)	**Met-min/wk**	845.8 (641.7)	1034.4 (1195.2)	575.0 (428.1)	0.110
Food intake; mean (SD)	**Kcal/day**	1496.7 (504.6)	1379.8 (392.6)	1272.4 (496.1)	0.205
Gender; N (%)	**Male**	9 (32.1)	13 (46.4)	9 (32.1)	0.441
	Female	19 (67.9)	15 (53.6)	19 (67.9)	
Education; N (%)	**≥ diploma**	14 (50.0)	16 (57.1)	22 (78.6)	0.072
	> diploma	14 (50.0)	12 (42.9)	6 (21.4)	
Hospitalization; N (%)	**No**	17 (60.7)	17 (60.7)	14 (50.0)	0.646
	Yes	11 (39.3)	11 (39.3)	14 (50.0)	
Surgery; N (%)	**No**	14 (50.0)	16 (57.1)	12 (42.9)	0.565
	Yes	14 (50.0)	12 (42.9)	16 (57.1)	
Drug; N (%)	**No**	20 (71.4)	18 (64.3)	25 (89.3)	0.084
	Yes	8 (28.6)	10 (35.7)	3 (10.7)	
Supplementation; N (%)	**No**	18 (64.3)	15 (53.6)	7 (25.0)	0.010
	Yes	10 (35.7)	13 (46.4)	21 (75.0)	

N: number; SD: standard deviation; met: Metabolic equivalent task; min: minute; wk: week.

Table 2

Comparison of the effects of MIND diet on Metabolic Syndrome indices between three studied groups (n = 84), Data are shown as Mean (SD).

Variable	Before				After				Effect size (ES)	Adjust[1] p-value
	MIND-propolis-1	MIND-placebo-2	Placebo-3	Crude-p-value*	MIND-propolis-1	MIND-placebo-2	Placebo-3	Crude-p-value*		
Weight (Kg)	76.4 (10.8)	80.8 (11.8)	79.5 (9.8)	0.280	74.8 (11.1)	80.02 (11.9)	79.5 (10.04)	0.235	$ES_{(1, 3)} = 0.97$ (0.95–0.99)	0.014
									$ES_{(2, 3)} = 0.98$ (0.96–1.00)	0.055
BMI (Kg/m$^{2)}$)	29.2 (4.3)	29.8 (5.3)	30.8 (3.9)	0.293	28.6 (4.5)	29.5 (5.2)	30.8 (3.9)	0.119	$ES_{(1, 3)} = 0.97$ (0.95–0.99)	0.019
									$ES_{(2, 3)} = 0.98$ (0.95–0.99)	0.027
WC (*Cm*)	98.1 (8.5)	99.1 (8.8)	110.9 (10.4)	0.769	96.6 (8.5)	97.2 (8.3)	100.7 (11.3)	0.415	$ES_{(1, 3)} = 0.98$ (0.96–0.99)	0.038
									$ES_{(2, 3)} = 0.98$ (0.96–0.99)	0.026
SBP (mmHg)	125.6 (14.1)	123.7 (12.9)	124.8 (17.6)	0.783	118.3 (13.8)	119.7 (11.2)	125.8 (15.5)	0.050	$ES_{(1, 3)} = 0.93$ (0.89–0.97)	0.002
									$ES_{(2, 3)} = 0.95$ (0.92–0.99)	0.021
DBP (mmHg)	79.6 (8.0)	79.8 (10.3)	79.6 (9.9)	0.976	75.9 (8.4)	75.6 (9.6)	81.6 (10.3)	0.036	$ES_{(1, 3)} = 0.94$ (0.89–0.98)	0.008
									$ES_{(2, 3)} = 0.92$ (0.87–0.96)	<0.001
FBS (m g/dL)	104.4 (14.8)	113.3 (12.5)	107.4 (12.1)	0.070	99.4 (16.4)	105.5 (11.8)	126.2 (36.9)	0.001	$ES_{(1, 3)} = 0.85$ (0.77–0.92)	<0.001
									$ES_{(2, 3)} = 0.83$ (0.76–0.90)	<0.001
TG (m g/dL)	235.8 (184.7)	195.3 (95.9)	183.8 (91.7)	0.307	157.7 (54.5)	143.2 (65.6)	180.0 (85.1)	0.038	$ES_{(1, 3)} = 0.75$ (0.63–0.89)	<0.001
									$ES_{(2, 3)} = 0.71$ (0.60–0.83)	0.001
HDL-C (mg/dL)	39.4 (9.5)	36.04 (4.7)	39.00 (6.7)	0.242	46.3 (7.9)	45.1 (7.0)	40.3 (9.1)	0.004	$ES_{(1, 3)} = 1.17$ (1.07–1.28)	0.001
									$ES_{(2, 3)} = 1.21$ (1.11–1.32)	<0.001
MIND-score (0–14)	7.04 (1.6)	7.2 (2.0)	6.7 (1.8)	0.552	12.2 (1.3)	12.4 (1.03)	7.7 (1.5)	<0.001	$ES_{(1, 3)} = 1.59$ (1.49–1.69)	<0.001
									$ES_{(2, 3)} = 1.59$ (1.50–1.68)	<0.001

*: Using Kruskal-Wallis test

[1]Using Generalized Linear Model (GLM) with distribution of Gamma & link of Log controlling for baseline, gender, education, surgery, drug, supplementation, physical activity, age, hospitalization, and food intake

BMI: Body Mass Index; WC: Waist Circumference; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; FBS: Fasting Blood Sugar; TG: Triglyceride; HDL-C: High-Density Lipoprotein Cholesterol; MIND: Mediterranean-DASH Intervention for Neurodegenerative Delay; ES: Effect Size; CI: Confidence Interval; SD: Standard Deviation.

Table 3
The MIND scores of before and after study and Adherence to the MIND diet.

Variable		Before				After			
		MIND-propolis	MIND-placebo	Placebo	p-value	MIND-propolis	MIND-placebo	Placebo	p-value
Green vegetable; N (%)	**≥ 2s/w**	13 (46.4)	12 (42.9)	13 (46.4)	0.919	0 (0.0)	0 (0.0)	6 (21.4)	<0.001
	2–6/w	9 (32.1)	7 (25.0)	8 (28.6)		3 (10.7)	1 (3.6)	9 (32.1)	
	≥ 6s/w	6 (21.4)	9 (32.1)	7 (25.0)		25 (89.3)	27 (96.4)	13 (46.4)	
Vegetable; N (%)	**≥ 5s/w**	13 (46.4)	9 (32.1)	14 (50.0)	0.580	0 (0.0)	0 (0.0)	8 (28.6)	<0.001
	5–7/w	3 (10.7)	5 (17.9)	5 (17.9)		1 (3.6)	0 (0.0)	6 (21.4)	
	≥ 1 s/d	12 (42.9)	14 (50.0)	9 (32.1)		27 (96.4)	28 (100)	14 (50.0)	
Berry; N (%)	**≥ 1s/w**	21 (75.0)	23 (82.1)	27 (96.4)	0.062	6 (21.4)	2 (7.1)	27 (96.4)	<0.001
	1–2/w	6 (21.4)	2 (7.1)	1 (3.6)		2 (7.1)	1 (3.6)	1 (3.6)	
	≥ 2s/w	1 (3.6)	3 (10.7)	0 (0.0)		20 (71.4)	25 (89.3)	0 (0.0)	
Nuts; N (%)	**< 1/m**	6 (21.4)	11 (39.3)	12 (42.9)	0.460	1 (3.6)	1 (3.6)	10 (35.7)	<0.001
	1/m to < 5/w	11 (39.3)	10 (35.7)	9 (32.1)		0 (0.0)	2 (7.1)	9 (32.1)	
	≥ 5s/w	11 (39.3)	7 (25.0)	7 (25.0)		27 (96.4)	25 (89.3)	9 (32.1)	
Olive oil; N (%)	**Not primary oil**	22 (78.6)	23 (82.1)	25 (89.3)	0.549	7 (25.0)	6 (21.4)	25 (89.3)	<0.001
	primary oil used	6 (21.4)	5 (17.9)	3 (10.7)		21 (75.0)	22 (78.6)	3 (10.7)	
Butter; N (%)	**> 2 tsp/d**	3 (10.7)	5 (17.9)	4 (14.3)	0.874	0 (0.0)	0 (0.0)	4 (14.3)	0.009
	1–2 tsp/d	5 (17.9)	5 (17.9)	7 (25.0)		2 (7.1)	3 (10.7)	7 (25.0)	
	< 1 tsp/d	20 (71.4)	18 (64.3)	17 (60.7)		26 (92.9)	25 (89.3)	17 (60.7)	
Cheese; N (%)	**≥ 7s/w**	10 (35.7)	5 (17.9)	0 (0.0)	0.002	2 (7.1)	2 (7.1)	7 (25.0)	0.222
	1–7/w	15 (53.6)	22 (78.6)	21 (75.0)		17 (60.7)	16 (57.1)	15 (53.6)	
	< 1s/w	3 (10.7)	1 (3.6)	7 (25.0)		9 (32.1)	10 (35.7)	6 (21.4)	
Wholegrains; N (%)	**< 1 s/d**	16 (57.1)	12 (42.9)	10 (35.7)	0.579	0 (0.0)	0 (0.0)	4 (14.3)	<0.001
	1–3/d	10 (35.7)	14 (50.0)	16 (57.1)		2 (7.1)	3 (10.7)	14 (50.0)	
	≥ 3 s/d	2 (7.1)	2 (7.1)	2 (7.1)		26 (92.9)	25 (89.3)	10 (35.7)	
Fish; N (%)	**Rarely**	19 (67.9)	16 (57.1)	17 (60.7)	0.668	7 (25.0)	5 (17.9)	15 (53.6)	0.006
	1–3/m	4 (14.3)	8 (28.6)	8 (28.6)		7 (25.0)	9 (32.1)	10 (35.7)	
	≥ 1 meals/w	5 (17.9)	4 (14.3)	3 (10.7)		14 (50.0)	14 (50.0)	3 (10.7)	
Bean; N (%)	**< 1 meals/w**	10 (35.7)	12 (42.9)	10 (35.7)	0.528	1 (3.6)	2 (7.1)	5 (17.9)	<0.001
	1–3/w	16 (57.1)	12 (42.9)	17 (60.7)		6 (21.4)	5 (17.9)	19 (67.9)	
	> 3 meals/w	2 (7.1)	4 (14.3)	1 (3.6)		21 (75.0)	21 (75.0)	4 (14.3)	
Poultry; N (%)	**< 1 meal/w**	8 (28.6)	6 (21.4)	9 (32.1)	0.719	2 (7.1)	2 (7.1)	5 (17.9)	0.040
	1–2/w	8 (28.6)	10 (35.7)	11 (39.3)		3 (10.7)	7 (25.0)	11 (39.3)	
	≥ 2 meals/w	12 (42.9)	12 (42.9)	8 (28.6)		23 (82.1)	19 (67.9)	12 (42.9)	
Meat; N (%)	**>6 meal/w**	0 (0.0)	0 (0.0)	0 (0.0)	0.163	0 (0.0)	0 (0.0)	0 (0.0)	0.045
	4–6/w	2 (7.1)	2 (7.1)	6 (21.4)		0 (0.0)	0 (0.0)	3 (10.7)	
	< 4 meals/w	26 (92.9)	26 (92.9)	22(78.6)		28 (100)	28 (100)	25 (89.3)	
Fast-food; N (%)	**≥ 4 times/w**	0 (0.0)	1 (3.6)	0 (0.0)	0.306	0 (0.0)	0 (0.0)	0 (0.0)	0.004
	1–4/w	5 (17.9)	4 (14.3)	9 (32.1)		2 (7.1)	1 (3.6)	9 (32.1)	
	< 1 time/w	23 (82.1)	23 (82.1)	19 (67.9)		26 (92.9)	27 (96.4)	19 (67.9)	
Sweet; N (%)	**≥ 7 s/w**	2 (7.1)	2 (7.1)	0 (0.0)	0.627	0 (0.0)	0 (0.0)	0 (0.0)	0.010
	5–7/w	10 (35.7)	8 (28.6)	11 (39.3)		3 (10.7)	2 (7.1)	10 (35.7)	
	< 5 s/w	16 (57.1)	18 (64.3)	17 (60.7)		25 (89.3)	26 (92.9)	18 (64.3)	

N: number; s: serving; w: week; d: day; m: month; tsp: tea spoon.

z_1 = Confidence Coefficient of 95 % of the study = 1.96
z_2 = Power factor of 80 % of the study = 0.84
s = Estimate of standard deviation = 16.7 = (100–0) 1/6 = (rang of NUCOG score divided to 6 = 16.7)
g = number of study groups = 3
d = to estimate the minimum average difference between two groups out of the three studied groups that make the difference meaningful = 14 [28].
For each of the intervention and control groups: n = 28 [28].

2.14. Information analysis methods and tools

The data obtained from the subjects was analyzed at two descriptive and analytic levels. The earlier reports include the result of descriptive analysis and tendency to the center and dispersion. Final analysis (including GLM analysis with distribution of Gamma & link of Log controlling for baseline, gender, education, surgery, drug, supplementation, physical activity, age, hospitalization, and food intake.

The Shapiro-Wilk test and examination of skewness were conducted to assess the normality of the distribution of quantitative variables. Quantitative variables were reported using either the mean (SD) or the median [interquartile Once were appropriated], while qualitative variables reported using the number (percentage). The estimated effect size and its 95 % confidence interval were presented for each outcome. Additionally, Chi-square tests were used for comparison. All two-tailed tests with a significance level of 0.05, and the Kruskal-Wallis test was used for the Crud-p value. The reporting of statistical results were adhered to the guidelines outlined in the SAMPL framework [29]. SPSS Statistics software version 26 was used for the statistical analysis of data.

3. Results

84 subjects in the age range of 18–60 years were recruited for this study. They were substituted into 3 groups (MIND diet + Propolis, MIND diet + placebo, and control groups) (28 people in each of the three groups). We were in contact with every single person. If they didn't answer, we would call them again and again, that's why we didn't have missing data in this study. The age, physical activity, food intake, gender, education, hospitalization, surgery, and drug between the three groups were not significantly different (p-value >0.05). The general characteristics of participants are shown in Table 1.

Mean before weight, BMI, WC, SBP, DBP, FBS, TG, and HDL-C hadn't shown a significant difference at the beginning (p-value >0.05). The metabolic syndrome indices are shown in Table 2.

At the beginning, there was a significant difference in dietary consumption between the three groups, only about the consumption of cheese. The MIND score was 7.04 (1.6), 7.2 (2.0), and 6.7 (1.8) in the MIND + Propolis group, MIND group, and control group, respectively, and there was no significant difference between the three groups (p-value >0.05). The MIND + Propolis and the MIND groups showed a significant increase in the MIND score which is near 1.59 times after adjusting variables (p-value < 0.001). Adherence to the MIND diet in three groups before and after the study is shown in Table 2. In the MIND + Propolis and MIND groups, the participants showed more adherence to the dietary compound consumption than the control group, which was significant for most items except cheese (Table 3).
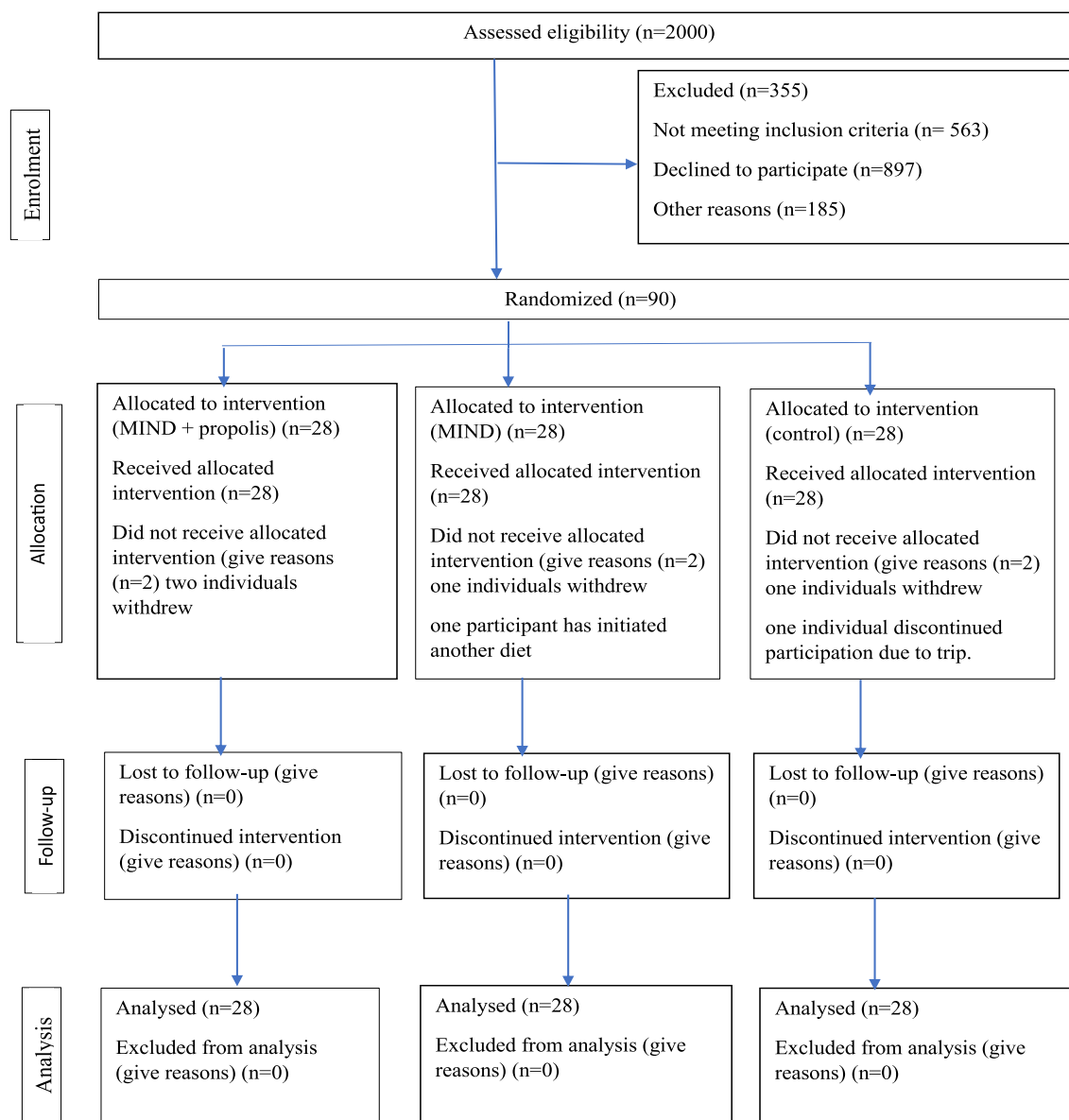
3.1. MIND group

In this study MIND group compared to control group after adjusting variables showed significant decrease (p-value < 0.05) about BMI (Kg/m2), WC (cm), and SBP (mmHg) by 0.98 times (2%), 0.98 times (2%), and 0.95 times (5%), respectively; this significant change (p-value < 0.001) was also observed in DBP (mmHg), FBS (mg/dl), and TG (mg/dl) by 0.92 times (8%), 0.83 times (17%), and 0.71 times (29%), respectively; HDL-C (mg/dl) has shown a significant increase (p-value < 0.001) by 1.21 times (21%), and weight (kg) has shown a non-significant decrease (p-value = 0.055) by 0.98 times (2%) (Table 2).

3.2. MIND + propolis group

MIND + Propolis group compared to control group after adjusting variables showed significant decrease (p-value < 0.05) in weight (kg), BMI (Kg/m^2), WC (cm), SBP (mmHg), DBP (mmHg), and TG (mg/dl) by 0.97 times (3%), 0.97 times (3%), 0.98 times (2%), 0.93 times (7%), 0.94 times (6%), and 0.75 times (25%), respectively; this significant change was also observed in FBS (mg/dl) (p-value < 0.001) by 0.85 times (15%), and HDL-C (mg/dl) has shown a significant increase (p-value < 0.05) by 1.17 times (17%) (Table 2).

No serious adverse effects or toxicity was reported in this study.

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┌─────────────────────────────────────────────────────────────────────────┐
│                      Assessed eligibility (n=2000)                        │
└─────────────────────────────────────────────────────────────────────────┘
                                          ┌──────────────────────────────────────┐
                                          │ Excluded (n=355)                      │
                                          │ Not meeting inclusion criteria (n= 563)│
                                          │ Declined to participate (n=897)       │
                                          │ Other reasons (n=185)                 │
                                          └──────────────────────────────────────┘
┌─────────────────────────────────────────────────────────────────────────┐
│                          Randomized (n=90)                                │
└─────────────────────────────────────────────────────────────────────────┘
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Allocated to intervention (MIND + propolis) (n=28)	Allocated to intervention (MIND) (n=28)	Allocated to intervention (control) (n=28)
Received allocated intervention (n=28)	Received allocated intervention (n=28)	Received allocated intervention (n=28)
Did not receive allocated intervention (give reasons (n=2) two individuals withdrew	Did not receive allocated intervention (give reasons (n=2) one individuals withdrew one participant has initiated another diet	Did not receive allocated intervention (give reasons (n=2) one individuals withdrew one individual discontinued participation due to trip.

Lost to follow-up (give reasons) (n=0)	Lost to follow-up (give reasons) (n=0)	Lost to follow-up (give reasons) (n=0)
Discontinued intervention (give reasons) (n=0)	Discontinued intervention (give reasons) (n=0)	Discontinued intervention (give reasons) (n=0)

Analysed (n=28)	Analysed (n=28)	Analysed (n=28)
Excluded from analysis (give reasons) (n=0)	Excluded from analysis (give reasons) (n=0)	Excluded from analysis (give reasons) (n=0)

Enrolment · Allocation · Follow-up · Analysis

CONSORT flowchart of participants throughout the study.

4. Discussion

Eighty-four subjects ranging aged 18 to 60 years were recruited in this study. They were substituted into 3 groups (28 people in each of the three groups). The age, physical activity, food intake, gender, education, hospitalization, surgery, drug, and supplementation between the three groups were not significant different. Mean before weight, BMI, WC, SBP, DBP, FBS, TG, and HDL-C hadn't shown significant differences at the beginning.

At the beginning, there was a significant difference in dietary consumption between the three groups (only about the consumption of cheese). There was no significant MIND score difference in between the three groups. The MIND + Propolis and MIND groups showed a significant increase in the MIND score. In the MIND + Propolis and MIND groups, the participants showed more adherence to the dietary compound consumption than the control group, which was significant for most items except cheese.

In this study the MIND and the MIND + Propolis groups compared to the control group showed significant decrease in BMI, WC, SBP,TG, and weight (non-significant for MIND group). This significant change was also observed in DBP and FBS, and HDL-C has shown a significant increase. No serious adverse effects or toxicity was reported in this study.

According to PM, by incorporating Fine-Humor Production into diets, we can promote the health of children, the elderly, and

mothers during pregnancy and nursing. It can help prevent chronic diseases and aid in recovery during illness, acute phases of disease, anemia, and metabolic conditions. Fine-Humor Production include MIND diet components like vegetables, fish, olive oil, berries, and nuts [30].

The Academy of Nutrition and Dietetics appointed a task force to create CAM competencies for dietetics practitioners. Education is necessary in this field, and the dietetics profession can lead the way in educating RDNs about the importance of functional foods, dietary supplements, and herbs in promoting health [31].

In ancient Persia, they called oxymel drink serkangabin, which comes from combining two words, serkeh (vinegar) and angabin (honey), because vinegar, honey/sugar, and water are the primary ingredients of oxymel that is PM. Oxymel seems to be a valuable functional food for people who are in good health and could also be a promising and safe treatment for conditions like asthma, obesity, and type 2 diabetes [32].

A healthy lifestyle and diet with average to high protein, low refined carbohydrates, and high unsaturated fat are considered major options in metabolic syndrome management [33]. Positive lifestyle modifications, such as consistent moderate-intensity exercise in overweight persons or subjects who have glucose intolerance, reduce developing MetS, especially in high-risk groups [34]. Nutrients as the major factors contributing to MetS and obesity, are provided within the context of their diet. Several articles have studied the impact of healthy eating patterns, such as the DASH diet and MD, on MetS [4]. The MIND diet integrates components of the DASH and MD diets to protect cognitive function. According to the first MIND diet study, those who have the highest score showed a lower incidence of cardiovascular disease. MIND diet components include berries, nuts, green leafy vegetables, other vegetables, whole grains, beans, poultry, seafood, olive oil, and wine which are healthy food items. It also includes cheese, butter and margarine, red meat, sweets, fast food, and fried foods, which are considered unhealthy food items [7]. The MIND diet emphasizes green leafy vegetables and berries consumption. It also includes cakes and sweets, fast food, fried food, butter, or margarine which aren't observed in the MD or DASH diet [4].

One study showed a significant correlation between the MIND diet and decreasing HDL-C levels and general obesity [4]. However, there wasn't a significant correlation between the MIND diet and either central or general obesity in another study [6]. The CAV1 gene variant rs3807992, a genetic marker that may be used to identify people with an increased risk of metabolic disorders can be modified, and the MIND diet may help improve dyslipidemia [8]. A higher MIND diet score resulted in a decrease in the incidence of CVD by 16 %. It has been demonstrated that incorporating whole grains, leafy green vegetables, and beans into the MIND diet can reduce the incidence of cardiovascular diseases by 60 %, 45 %, and 65 %, respectively [35].

Propolis is a resinous substance that is produced by a combination of buds, and plant secretions with bees' salivary enzymes, it is a compound and sticky substance used in the hive [12,13]. In recent decades, propolis has attracted the attention of researchers due to several biological and medicinal properties such as immune modulator, anti-tumor, antimicrobial, anti-inflammatory, and antioxidant [14]. Some studies have shown significant reduction in serum fasting glucose levels, lipid profiles, HbA1c, insulin, insulin resistance, CRP, TNF-α, interleukin-6 and liver enzymes like Alanine transaminase and Aspartate aminotransferase after consuming propolis supplement [12,13] as well as increase in serum HDL-C [13]. Another study has shown a significant decrease in TG and an increase in HDL-C. However, no significant changes were observed for BMI, weight, total cholesterol and LDL-C [15]. Propolis can reduce leptin levels in people with central obesity [36]. The results of a meta-analysis have shown a significant reduction in HbA1c and fasting plasma glucose after propolis consumption. However, no significant reduction in fasting insulin levels and HOMA IR was observed [37]. A review study showed the effective role of propolis in the management of MetS and its indicators which may be related to its high anti-inflammatory and antioxidant potential [38].

The beneficial effects of the MIND diet may have been linked to the use of olive oil as the main source of dietary fats and phenolic compounds [39] that increases HDL-C cholesterol and protect blood lipids from oxidative stress [40]. MUFA of olive oil in this diet decrease TG and increased HDL_C [41].

Dietary intake of OEA concentration by increasing substrate availability for OEA biosynthesis [42]. Oleic acid in olive oil triggers oleoylethanolamide, which is one of the intestinal satiety messengers in the brain [43]. MIND diet leads to a decrease of WC, because of its components and special elements like intake of less high-calorie-dense foods [44], low-glycemic index foods, high dietary fiber, low glycemic load and being plant-based [45]. High fiber content reduces the rate of carbohydrates absorption in the gastrointestinal tract and decrease the glycemic index [46]. High levels of potassium, magnesium, vitamin C, and phytochemicals in this diet are associated with decreased insulin resistance which is a major factor in metabolic disorders among overweight and obese people [47]. The source of phytochemicals, fiber, and antioxidants are fruits especially berries that can decrease weight [48]. Flavonoids may have a role in adipocyte differentiation, glucose tolerance, lipid metabolism, insulin sensitivity, inflammatory status, and oxidative stress [49,50]. Consumption of berries decreases blood pressure significantly [51,52]. Low amounts of red meat and saturated fatty acid content of the MIND diet improve glucose metabolism, cardiovascular risk factors, and body weight [53]. Additionally, the consumption of green leafy vegetables and whole grains has anti-inflammatory and anti-oxidative effects, which may have negative effect on serum concentrations of Leptin and Ghrelin concentration [54].

One possible explanation for the positive effect of propolis on the lipid profile may be increased expression of ATP-binding cassette transporters in liver proteins, which are known to be linked to the formation of HDL-C and the efflux of lipids from peripheral tissues [55,56]. Conversely, propolis may enhance the activation of the ABCA1 pathway by stimulating PPAR gamma and liver X receptor expression. This stimulation can subsequently result in a decrease in cholesterol accumulation within macrophage foam cells [57]. The potential mechanisms responsible for the hypoglycemic effect of propolis may be ascribed to the presence of bioactive constituents in propolis, which have the potential to enhance insulin production and/or augment cellular responsiveness to insulin [58]. Propolis has the potential to enhance the uptake of glucose and the movement of insulin-sensitive GLUT 4 in skeletal muscle cells through the activation of PI3K and AMPK phosphorylation, thereby promoting cellular glucose utilization [59]. Moreover, propolis can suppress

the activity of genes involved in gluconeogenesis, particularly glucose-6-phosphatase, in hepatocellular cells within the liver [60]. Propolis seems to hinder the progression and expression of MetS through three mechanisms: suppressing the expression of AGEs and RAGEs, reducing pro-inflammatory signaling pathways, and enhancing the cellular antioxidant systems [38].

4.1. Strengths and limitations

Strengths: (a) This study is the first investigation that was designed to evaluate the effect of the MIND diet and Propolis supplementation on metabolic syndrome indices among metabolic syndrome subjects. Randomized control trial; (b) blood sampling and measuring biochemical parameters in the laboratory of the same Health Center where the participants were selected and studied. However, the current study had some limitations: (a) due to budget constraints; (b) we were unable to measure some factors (such as antioxidants) and other inflammatory biomarkers. (c) The duration of the study was not long, and it may have had considerable effects on our results.

5. Conclusion

This study investigates the influence of the MIND diet and Propolis on metabolic syndrome indices. Accordingly, we found that the MIND diet + Propolis supplement and MIND diet compared to the control group can decrease significantly weight, BMI, WC, SBP, DBP, FBS, TG and significantly increases HDL-C. In this study, patients reported the benefits of the MIND diet and consumption of propolis in relieving constipation and its complications. We suggest that the MIND diet and propolis be investigated for their other clinical potential effects.

Approval of the submission

Z.P and all authors have read and approved the final version of the manuscript have full access to all of the data in this study, and take complete responsibility for the integrity of the data and the accuracy of the data analysis.

Funding

Originality

Acknowledgement of sources

We ensure that give credit to our colleagues and cite relevant previously published work appropriately.

Duplicate publication

This study has not been published previously, and that it is not under consideration for publication elsewhere.

Related work

we didn't publish the results and conclusions of a single study in multiple papers.

Data availability statement

The datasets generated and/or analyzed during the current study are not publicly available due to some restrictions applied by the ethics committee; data associated with our study have not been deposited into a publicly available repository, but data will be made available on request. The questionnaires are available in Persian upon request.

Ethics declarations

Ethics and consent statement

The present study is in agreement with the Declaration of Helsinki and its later amendments and has received prior approval from the Medical Ethics Committee of Isfahan University of Medical Sciences, with an ethics code of IR.MUI.RESEARCH.REC.1401.330 with grant no. 3401567. Before enrollment, written and verbal informed consent was obtained from all the participants. All patients provided written informed consent to participate in the study and for their data to be published. All patients provided written informed consent for the publication of their anonymised case details and images. All patients were informed that consent to participate in the study and publish their data would be assumed on completion and submission of the study questionnaire/survey. The Iranian Registry

of Clinical Trials (www.irct.ir), which has the registration reference IRCT20230105057054N1, approved the protocol for the current study on March 28, 2023.

Consent for publication

Not applicable.

Transparency statement

The primary author, Z.P, confirms the present study's report's authenticity, accuracy, and transparency. Moreover, no crucial elements of the research have been omitted, and any deviations from the original study design (if applicable, registered) have been clarified.

Authorship contribution statement

Zainab Gholami: Writing – original draft, Validation, Software, Resources, Project administration, Methodology, Investigation. **Mohammad Reza Maracy:** Validation, Formal analysis. **Zamzam Paknahad:** Writing – review & editing, Visualization, Validation, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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