STUDY PROTOCOLS

# Effects of MIND diet and propolis supplementation on metabolic syndrome indices and cognitive function among patients with metabolic syndrome in Isfahan, Iran, 2024. A rationale and study protocol for randomized controlled trial

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## Abstract

Metabolic syndrome (MetS) is the main general and clinical health challenge worldwide. Based on the National Cholesterol Education Program, if the person has three or more indices containing: elevated fasting blood sugar, high levels of triglycerides, hypertension, low levels of high-density lipoprotein cholesterol, and central obesity, he suffers MetS. The Mediterranean-Dietary Approaches to Stop Hypertension (DASH) Intervention for Neurodegenerative Delay diet is a novel diet that with the specific aim of safeguarding cognitive function.

Propolis is a resinous substance produced by bees from the combination of buds and secretions of plants with saliva and bee enzymes. After propolis supplementation, a significant reduction in fasting plasma glucose levels and lipid profiles has been observed.

Considering the importance of chronic diseases like MetS on health, the role of the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet and propolis supplement that will improve blood sugar, blood lipid, anthropometric indicators, blood pressure, and cognitive function, and limited contradictory studies, we decided to conduct this study. This study, which is a randomized controlled clinical trial study, will be conducted on adults with MetS who will visit Hazrat Ali Health Center in Isfahan. Participants must provide informed consent before engaging in the study. Demographic data such as age, gender, and medical history will be recorded. Then, anthropometric indices, MetS indices, and cognitive function will be measured in all subjects.

The study participants will be divided into three groups and will be controlled for 12 weeks. We will have a MIND diet + placebo group, a MIND diet + propolis supplement group, and a control group that will receive a microcrystalline cellulose placebo and usual dietary advice. At the end of the intervention, all indices will be assessed again.

## 1 | BACKGROUND

Metabolic syndrome (MetS) is characterized by a combination of factors that are indicative of the increasing prevalence of abdominal obesity worldwide.[1] MetS includes a cluster of metabolic abnormalities that confer an increased risk for cardiovascular disease (CVD) and type 2 diabetes. Based on National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III), if the person has three or more of these indications including fasting blood sugar (FBS), hypertriglyceridemia, hypertension, low high-density lipoprotein cholesterol (HDL-C), and central obesity known as having MetS. The most important factor that contributing the high prevalence of MetS is obesity. The incidence of MetS has been correlated with augmented proportions of obesity.[2-5]

The frequency of MetS occurrence increases significantly with age between all subgroups. The prevalence among 20–39-year-olds and 60-year-olds is 19.5% and 48.6%, respectively.[4] The general estimate of the prevalence of MetS is 30.4%, and results from numerous studies have revealed that around one-third of Iranian adults aged 20 and older MetS, and the prevalence rate rises with age.[6] The high consumption of high-calorie foods and refined carbohydrates such as rice and bread, which is one of the eating habits of Iranians, may be the reason for the high prevalence of obesity.[7]

A diet with an average amount of mostly unsaturated fat, a lower amount of refined carbohydrates, an average to a high number of proteins, a high amount of fiber, fish consumption, and lifestyle changes can be effective in the treatment of MetS.[8] The major factors involved in MetS and obesity are nutritional factors and how people get nutrients in the context of their diet, several articles have investigated the effects of healthy eating patterns, including the Dietary Approaches to Stop Hypertension (DASH) diet as well as the Mediterranean diet (MD), on the MetS.[5]

The Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet combines elements of the MD and DASH diets and has been developed to protect cognitive function. Individuals with the most elevated MIND diet scores exhibit a reduced incidence of CVD (the first MIND diet study). The components of the MIND diet include healthy food groups (green leafy vegetables, other vegetables, nuts, berries, beans, whole grains, seafood, poultry, olive oil, and wine) and five unhealthy food groups (red meat,

butter and margarine, cheese, sweets, fried foods, and fast food.[9] The MIND diet emphasizes the use of green leafy vegetables and berries. It has a category for Cakes and sweets, some items like fast foods, fried foods, and butter and margarine are not considered in the DASH or MD diet. One study found a significant association between adherence to the MIND diet and the probability of diminishing HDL-C levels and general obesity.[5] In one investigation, they didn't observe any significant association between the MIND diet and general or central obesity in adult populations.[7] Utilizing the MIND diet may promote improvements in dyslipidemia by modulating the Caveolin 1 (CAV1) gene variant rs3807992, which is a genetic marker that could be used to identify individuals with an increased risk of metabolic disorders.[10]

It has been found that The MIND dietary intervention may be effective in reducing the negative impact of obesity on cognitive function and brain structure. This intervention can be further optimized through the implementation of moderate caloric restriction.[11] Increasing the MIND diet score reduces the incidence of CVD by 16%. Incorporating whole grains, green leafy vegetables, and beans as part of the MIND diet has been shown to decrease the incidence of CVD by 60%, 45%, and 65%, respectively.[12] Favorable lifestyle changes, such as regular moderate-intensity physical activity in those with overweight and glucose intolerance, lead to a decrease in the probability of developing MetS, particularly within high-risk populations.[13] Following the MIND dietary pattern also is associated with less chance of disorder, a decrease in physical performance, and better muscle strength.[14] One study indicated that adherence to the MIND diet was associated with the reduce lipid profile and general obesity.[15] There was no significant correlation found between MIND and the prevalence of hypertension in the adult population.[16] Adhering more closely to the MIND diet was linked to reduced visceral fat and a lower prevalence of each MetS component in adult individuals.[17] The MIND diet was generally linked with improvement in anthropometric measures and other cardiometabolic outcomes, including blood pressure, glycemic control, lipid profile, inflammation, and stroke.[18] The MIND diet is a new dietary pattern that has been found to have potential as an anti-hypertensive intervention.[19] The MIND diet score is positively correlated with increased insulin sensitivity.[20]

The increasing prevalence of MetS and the rate of elderly people will have serious implications for health care. A proper diet and

increased physical activity reduce the risk of MetS, which controls and cures Alzheimer's disease.[21] MetS increases the risk of Alzheimer's disease in women but not in men.[22] Recent research shows a relation between brain dysfunction and the pathogenesis of the MetS. Refined carbohydrates, fat content, and type of fatty acids are all associated with a sedentary lifestyle and psychological stress, which can predispose to inflammation.[23] MetS affects cognitive function and brain structure negatively.[24] Obesity can lead to increased oxidative stress and inflammation, which have been shown to have a hurt cognitive and motor function in the brain. The MIND diet, which is rich in polyphenols and antioxidant compounds, has been shown to ameliorate these negative effects.[11]

Previous studies have shown that vitamin D[25] and blueberry supplementation[26] are useful options for the management of MetS in humans. Propolis is a resinous mixture composed of plant buds, secretions, and saliva, produced by salivary glands and bee enzymes, which is a complex and viscous substance employed by bees within their hives.[27,28] In recent decades, propolis has drawn the attention of researchers due to several biological and medicinal properties like immunomodulatory, antitumor, antimicrobial, anti-inflammatory, antioxidant, and so forth.[29]

The propolis supplementation resulted in a noteworthy significant decline in fasting plasma glucose levels, lipid profiles, hemoglobin A1C (HbA1c), insulin, insulin resistance, C-reactive protein, Tumor necrosis factor alpha, interleukin-6 and Alanine transaminase, Aspartate aminotransferase.[27,28] HDL-C increases significantly after consuming propolis.[28] A study has shown a significant decrease in triglyceride (TG) and an increase in HDL-C. However, no significant changes were observed for body mass index, weight, total cholesterol, and LDL-C.[30] Propolis can reduce leptin levels in people with central obesity.[31]

A meta-analysis revealed a significant decline in fasting plasma glucose levels and HbA1c with propolis consumption, however, there was no significant reduction in fasting insulin and Homeostatic Model Assessment for Insulin Resistance (HOMA IR) levels.[32] A review article exhibited the potential consumption of propolis in improving MetS and its symptoms, possibly due to its strong anti-inflammatory and antioxidant attributes.[33] The review article suggested that honey bee propolis is effective in enhancing cellular function and mitigating complications associated with diabetes.[34] One study demonstrated that propolis may be beneficial in reducing waist circumference (WC), albeit without exerting significant influence on other MetS components.[35] Propolis polyphenols have demonstrated potential effects on thermogenesis, browning, and fat metabolism, which may contribute to the regulation of body weight.[36]

The impact of chronic conditions like MetS on public health is proven. According to the role of the MIND diet and propolis supplementation in correcting MetS indices, and cognitive function, and because of limited contradictory studies about those subjects we decided to study the effects of MIND diet and propolis supplement consumption on MetS indicators (lipid profile, blood sugar, blood pressure, and WC) and cognitive function and compare its areas in people with MetS.

## 2 | METHOD

### 2.1 | Study goals

The purpose of this research study is a compare the effects of the MIND diet and propolis supplementation on MetS indices and cognitive function and its areas in people with MetS.

### 2.2 | Study design

This study is a parallel RCT.

We use CONSORT checklist as Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomized trials.[37]

### 2.3 | Study registration

The present study's protocol was approved by the Iranian Registry of Clinical Trials (www.irct.ir) on 3/28/2023 and a registration reference is IRCT20230105057054N1. The study was designed and reported in compliance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement. The SPIRIT flow diagram outlines the timeline for recruitment, interventions, and assessments and is presented in Figure 1.

### 2.4 | Study population

The population in this study will be adults (18–60 years old) who have MetS. To diagnose MetS based on guidelines NCEP ATP III will be performed. Adults with MetS who will be visited at Hazrat Ali Health Center in Isfahan.

### 2.5 | Inclusion and exclusion criteria

#### 2.5.1 | Inclusion criteria

1. Adults (18–60 years old).
2. Patients with MetS. To diagnose MetS according to on NCEPA ATP III.
3. Patients with MetS will be referred to Hazrat Ali Health Center in Isfahan.

#### 2.5.2 | non-entry criteria

1. Suffering from thyroid diseases, anemia, diabetes, neurological and psychiatric illnesses including depression, Parkinson's disease, Alzheimer's disease, mental disorders, and a history of severe medical treatment.

| | 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 | | * | | | | * |
| Cognitive function | | * | | | | * |
| Dietary intake | | * | | | | * |
| Physical activity | | * | | | | * |
| Possible side effect | | | * | * | * | |
| Participant compliance | | | * | * | * | |

**FIGURE 1** The SPIRIT figure outlines the enrollment, interventions, and assessments schedule according to the Standard Protocol Items: Recommendations for Interventional Trials. SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials.

2. Have a stroke or ischemic attack in the last 90 days.
3. History of brain damage, liver and kidney illnesses, hepatitis C or human immunodeficiency virus (HIV), and weight changes.
4. Have been diagnosed with cancer in the last 5 years.
5. Obese people with a BMI higher than 40.

### 2.5.3 | Exclusion criteria of samples

1. Noncooperation of participants in various stages of project implementation.
2. Get a specific diet.
3. Have an Allergy to propolis supplement.
4. Getting pregnant during the research.
5. Suffering from diseases like stroke, memory loss, or any other case where the person cannot interview.

6. Presence of other chronic diseases such as chronic liver cirrhosis, kidney failure, thyroid disease, inflammatory bowel disease, rheumatoid arthritis, severe heart failure, weakness, and thinness.
7. Blood clotting after consumption of propolis supplementation.

### 2.6 | Sample size and sampling method

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

$z_1$ = 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 of Neuropsychiatry Unit Cognitive Assessment (NUCOG) cognitive performance score = 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 (suggested by expert opinion).

For each of the intervention and control groups: $n = 28$.[38]

## 2.7 | Sampling

Adults with MetS who will visit Hazrat Ali Health Center in Isfahan, after the diagnosis of MetS, will be selected sequentially, if they meet the entry objects will be recruited.

First, the necessity of research and the importance of their presence in the current research will be explained to the subjects. Eligible individual will receive an informed consent form to participate in the plan.

In the process of allocating patients in three groups randomly in blocks of three, samples will be allocated in to the intervention and control groups using a randomized block design. 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."

The qualified subjects who have been referred will be placed in 28 blocks of three. The first 3, second 3, and 28th three eligible subjects are placed in the first, second, and 28th block respectively. For intervention and control groups (MIND diet + placebo, MIND diet + propolis supplement, and control) codes A, B, and C are considered. The subjects of each block are based on the table of random numbers, so that if the random number is 1–3, treatment A, if it is 4–6, treatment B, and if it is 7–9, treatment C (Random numbers generated by the computer can also be used for this purpose). Therefore, based on the received random number, the first person in the block is assigned to the treatment code corresponding to the random number. This process will continue until 28 blocks are completed, and then treatments A, B, and C will be assigned random numbers by the design expert. At this stage, Only the assigned expert will have knowledge of A, B, and C. Until all the subjects are enrolled in the study, the codes of A, B, and C will be opened. The expert does not have a role in grouping participants and does not group participants purposely and that the steps are done randomly and all patients will start 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

## 2.8 | Information collection methods

Demographic and health history information including age, sex, level of education, marital status, medical history, and use of drugs, supplements, and herbal medicines will be collected by interviewing and filling out the forms. Food intake, anthropometric indices, biochemical markers like blood sugar, lipid profile, blood pressure, and physical activity will be assessed in all subjects.

## 2.9 | Anthropometrics assessment

Anthropometric variables (height, weight, and WC) are measured and recorded by a trained person because these are one of MetS indices. The weight is measured without shoes, with minimal clothing, by a scale with an accuracy of 100 g, and the height is 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. To eliminate personal errors, the measurements will be done by two people (one person only for men and one person only for women). The body mass index (BMI) of subjects is calculated by dividing the weight (in kg) by the square of the height (m$^2$). Also, the WC is measured as an index of fat distribution, the person should be wearing minimal clothes, the place the inflexible meter 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.[39]

## 2.10 | Diagnosis of MetS

Diagnosing MetS is according to NCEP ATP III guidelines.[40] Coexistence of at least three of the following factors will be considered as MetS. These tests will be done for all subjects at the beginning and end of the study in a certain laboratory.

- TG exceeding 150 mg/dL.
- HDL_C levels less than 40 and 50 mg/dL in men and women, respectively.
- Systolic blood pressure (SBP) and diastolic blood pressure (DBP) greater than 130 and 85 mmHg, respectively.
- FBS above 100 mg/dL.
- WC above 102 and 88 cm in men and women, respectively.[41]

## 2.11 | Blood pressure measurement

SBP and DBP will be measured with a calibrated sphygmomanometer in a sedentary position because these are MetS indices, three times at 5-min intervals after filling two-thirds of the questionnaire and after about 40 min of rest. Then the mean of the second and third numbers will be recorded as blood pressure.[41]

## 2.12 | Measurement of biochemical factors

To determine FBS, TG, and HDL-C concentrations, blood samples will be collected after 12 h of fasting at Hazrat Ali Health Center in Isfahan. We will measure these factors because these are MetS

indices. We ask the participants not to take part in vigorous physical activity, alcohol, or caffeinated drinks 24 h before the blood sampling.

All laboratory measurements will be performed according to a standard protocol using an auto-analyzer.

## 2.13 | Evaluation of cognitive performance and its areas

All patients will undergo cognitive evaluation, which will be done by a psychologist and this is one of our outcomes. The NUCOG test will be used to assess the cognitive status of patients, which places patients in five cognitive domains, including attention, visuospatial, memory, executive function, and language. NUCOG is a 21-part tool that examines a broad confine of cognitive functions. The score of this test in each domain is considered 0–20 and the highest total score will be 100. The Persian version of this test was found valid in previous research and its Cronbach's alphas' reliability coefficient was calculated as 0.919.[42] The diagnostic accuracy of dementia using a cumulative score of 80 in the NUCog assessment tool yielded a sensitivity and specificity of 0.84 and 0.86, respectively.[43,44]

The domains of cognitive function include the following:

Attention: Orientation of time and place, numbers, reverse sequence.

Spatial vision: graphical representation, functional, right and left orientation, negation, and calculation.

Memory: verbal recording, verbal recall, spatial recall, and remote memory.

Executive function: sequencing, classification, abstract thinking, manipulation.

Language: understanding the concept, repeating, naming and writing, reading and finding words.[45]

## 2.14 | Dietary assessment

The dietary intake of subjects will be determined by using a 3-day food record because the food intake of the patients should remain constant during the study. In this manner, each subject will record the detailed food consumed during two working days and 1 day off. That is,: 10th, 50th, and 73rd days. Then, The dietary information will be extracted using Nutritionist IV software version 3.5.2, and the amount of energy consumption, macronutrients, and micronutrients will be determined.[46]

## 2.15 | Assessment of physical activity

The type and amount of physical activity per day for each person will be recorded and converted into a metabolic equivalent[47] Because the physical activity of patients should remain constant during the study. Individuals are not advised on the amount of physical activity, and we ask individuals to continue the same physical activity process as before.

## 3 | INTERVENTION

One of the groups which will be administered the MIND diet along with a placebo, and the other which will be given a combination of the MIND diet and propolis supplement will be considered as intervention groups. The next group will receive a microcrystalline cellulose placebo + usual dietary advice is the control group. We use microcrystalline cellulose as a placebo because it is a white, neutral, nonreactive, insoluble, free-flowing versatile excipient.[48] Two intervention groups will be given the regular food recommendations as well as the control group, any calorie restriction will be considered for each of the three groups. To avoid bias, the person who will collect data will be different from who will deliver the intervention.

After the classification, recruited subjects will cooperate for a 12-week duration. To determine compliance, patients will be asked to record at least 3 dietary intakes (2 days on weekdays and 1 day on weekends) and communicate with us weekly by phone and in person (in the last week). Subjects who have filled at least 70% of dietary records (i.e., 2 out of 3 records) will be considered qualified, and daily self-monitoring strategies (to persuade adherence to the prescribed diet and nutritional recommendations) will be taught to the subjects. Motivational strategies including newsletters and website activities will be implemented to increase patients.

The first individual visit will include basic diet education, advice on common dietary recommendations, and receiving supplements, which will be done for the three groups separately.

## 3.1 | MIND diet group

This intervention will be to investigate the effect of the MIND diet on the indicators of MetS and cognitive function. The counseling plan for the intervention diet group will include instructions on what foods to include in the diet, and the paths to provide these foods.

The MIND diet is extracted from Morris. Participants in the MIND diet group will receive instructions to modify their dietary content, emphasizing natural and plant-based foods and consuming berries and green leafy vegetables, whole grains, fish, nuts, and olive oil, and with restricted consumption of animal food and high saturated fat is recommended. According to Islamic customs and culture, the people of Iran are bound not to consume alcoholic beverages, so, we persuade our patients to use grapes, grape juice, and raisins for correcting.[49] For each person, the MIND diet will be provided specifically for 7 days a week along with counseling for at least 30 min, and people will be asked to visit the relevant center for 3 days (Days 7, 45, and 80 of the study), and the minimum time for counseling and checking compliance with the diet in each meeting will be 15 min for each person. An example of the MIND diet with 2000 kcal of energy is given in. In addition, routine dietary advice will be used, which will include verbal and written general data about healthy food selections according to the healthy food plate (50–60% carbohydrates, 5–20% protein, and 30% fat). All participants will get acquainted with the principles of food recommendations, which are as follows:

- Eat slowly and chew your food completely and with pleasure.
- Instead of frying foods, use steamed, boiled, and grilled foods.
- Take off any excess fat and skin from your chicken or meat before cooking.
- Use whole-meal bread and mixed oats and rice instead of simple rice and pasta.
- Refrain from removing any meals.
- Eat frequent but small meals.
- Try to limit your intake of sugary and fatty foods.

This combination is more similar to the food pattern of Iranians.[46]

Microcrystalline cellulose placebo will also be used in this group, the drug and placebo will be completely similar and will be prepared in the Department of Pharmacology of Mashhad University of Medical Sciences and none of the participants and researchers will know about them until the end of the study.

Participants will be trained to diet on their own. Each week, adherence to the dietary intervention will be measured through the assessment of the MIND diet score questionnaire and the food record. Patients who meet the criteria for 80% or more of their meals and snacks will be considered as adhering to the MIND diet.[49]

## 3.2 | Components of the MIND diet

Healthy food groups (green leafy vegetables, other vegetables, nuts, berries, beans, whole grains, seafood, chicken, olive oil, and wine) and 5 unhealthy food groups (red meat, butter and margarine, cheese, sweets, and fried foods, and fast food). The points are based on 0, 0.5, or 1 and the total score of the MIND diet will be calculated by adding them up and is a maximum of 15 points.

If olive oil, is the main edible for the subjects, it has a score of 1 and otherwise a score of 0, and for other components of the dietary score, we will summarize the frequencies of food consumption.[9]

### 3.2.1 | MIND diet + propolis group

This intervention will investigate the effect of the MIND diet and propolis supplementation on the indicators of MetS and cognitive function. The MIND diet + propolis group will be advised of the usual food recommendations related to the first group. The propolis supplement will be prepared in the Department of Pharmacology of Mashhad University of Medical Sciences. They will receive (450 mg twice daily before lunch and dinner)[50] for 12 weeks. The dosage of propolis is based on the selection of a phase II trial.[51]

### 3.2.2 | Compliance of the subjects

Subjects will be referred to at the onset, midpoint, and conclusion of the study. Also, the regular consumption of the supplement will be followed weekly through telephone calls and text messages. In addition, people will be requested to note their daily consumption by ticking the embedded table. Apart from this, at the end of the study, the unused amount of the supplement packaging received from the patients will be calculated. To make sure that the patients follow the mind diet and take the propolis supplement on time, we will do the above.

### 3.2.3 | Control group

This group will be the control group to compare with the two intervention groups. Routine dietary advice will be offered to the Control group subjects which will include oral and written information about to ensure the diet is balanced and aim for healthy food choices that follow the guidelines of the healthy food plate. This means consuming around 50–60% carbohydrates, 5–20% protein, and 30% fat. In this case, none of the participants will receive food menus and will get to know the food recommendations, as follows:

- Eat slowly and chew your food completely and with pleasure.
- Instead of frying foods, use steamed, boiled, and grilled foods.
- take off any excess fat and skin from your chicken or meat before cooking.
- use whole-meal bread and mixed oats and rice instead of simple rice and pasta.
- refrain from removing any meals.
- Eat frequent but small meals.
- Try to limit your intake of sugary and fatty foods.[46]

In addition to the usual food recommendations, the microcrystalline cellulose placebo will be offered. The placebo which is completely similar to propolis, will be prepared in the Department of Pharmacology of Mashhad University of Medical Sciences and none of the subjects and researchers will distinguish them until the end of the study.

After 12 weeks of intervention, we will ask the participants not to do severe physical activity and not to drink alcohol and caffeinated drinks for 24 h, and then measure anthropometric data, MetS indices, and cognitive function and its domains.

## 4 | INFORMATION ANALYSIS METHODS AND TOOLS

The data obtained from the subjects will be analyzed in two descriptive and analytic levels. The earlier includes the report of statistical summary indices including the criteria of the tendency to the center and dispersion. Tables and graphs, and the second includes primary analysis (including a paired $t$-tests and analysis of variance) and final analysis (including a generalized linear model 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 will be conducted to assess the normality of the distribution of quantitative variables. Quantitative variables will be reported using either the mean ± standard deviation or the median [interquartile Once were appropriated], while qualitative variables will be reported using the number (percentage). The estimated effect size and its 95% confidence interval will be presented for each outcome. The study will utilize paired *t*-test or Wilcoxon signed-rank test for quantitative variables to compare differences within groups. Additionally, Chi-square tests will be used for comparison. The independent *t*-test or Mann–Whitney *U* test will be utilized to compare differences between groups in quantitative variables. The study will utilize the Pearson $\chi^2$ test or Fisher's exact test to assess differences between groups in qualitative variables. All tests will be two-tailed with a significance level of 0.05, and the Kruskal–Wallis test will be used for the Crud-*p* Value. The reporting of statistical results will adhere to the guidelines outlined in the Statistical Analyses and Methods in the Published Literature (SAMPL) framework.[52] SPSS Statistics software version 26 will be used for statistical analysis of data. SPSS26 software Data analysis will be done by SPSS$_{26}$ software.

## 5 | DISCUSSION

A healthy life style and diet with average to high protein, low refined carbohydrate, and high unsaturated fat are considered major options in MetS management.[8] 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 CVD.[9] One study showed a significant correlation between the MIND diet and decreasing HDL-C levels and general obesity.[5]

Some studies have shown significant reduction in serum fasting glucose levels, lipid profiles, HbA1c, insulin, insulin resistance, after consuming propolis supplement[27,28] as well as increase in serum HDL-C.[28] 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.[30] Propolis can reduce leptin levels in people with central obesity.[31] The results of a meta-analysis have shown a significant reduction in HbA1c and fasting plasma glucose after propolis consumption.[32] 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.[33]

The MIND diet, which is rich in polyphenols and antioxidant compounds, has been shown to ameliorate negative effect on cognitive and motor function in the brain.[11] Propolis has been found to be beneficial in enhancing cognitive abilities, including memory, information processing, complex attention, and concentration among elderly individuals in Japan.[53] Older individuals residing at elevated altitudes experienced a progression to mild cognitive impairment within a period of 24 months, accompanied by an exacerbation of systemic inflammation. Consumption of propolis for more than 12 months provided protection against cognitive decline subsequent to the reduction in systemic inflammation.[54]

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 [55] that increases HDL-C cholesterol and protect blood lipids from oxidative stress.[56] MUFA of olive oil in this diet decrease TG and increased HDL_C.[57] MIND diet leads to a decrease of WC, because of its components and special elements like intake of less high-calorie-dense foods,[58] low-glycemic index foods, high dietary fiber, low glycemic load and being plant-based.[59] High fiber content reduces the rate of carbohydrates absorption in the gastrointestinal tract and decrease the glycemic index.[60] 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.[61] The source of phytochemicals, fiber, and antioxidants are fruits especially berries that can decrease weight.[62] Flavonoids may have a role in adipocyte differentiation, glucose tolerance, lipid metabolism, insulin sensitivity, inflammatory status, and oxidative stress.[63,64] Consumption of berries decreases blood pressure significantly.[65,66] Low amounts of red meat and saturated fatty acid content of the MIND diet improve glucose metabolism, cardiovascular risk factors, and body weight.[67] Additionally, the consumption of green leafy vegetables and whole grains has anti-inflammatory and antioxidative effects, which may have negative effect on serum concentrations of Leptin and Ghrelin concentration.[68]

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.[69,70] 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.[71] Propolis can suppress the activity of genes involved in gluconeogenesis, particularly glucose-6-phosphatase, in hepatocellular cells within the liver.[72]

It is suggested the antioxidant and anti-inflammatory properties of certain foods included in the MIND diet protect brain function and cognitive decline are responsible to these effects.[73,74] Green leafy vegetables are a source of folic acid, vitamin E, carotenoids and flavonoids reduce the risk of dementia and cognitive decline.[75] Reduced consumption of butter and margarine, sweets in according to limiting the saturated and trans fats effects improve blood-brain barrier function.[76] Vitamin E, found in vegetable oils, nuts and whole grains, has been shown to protect cognitive performance,[75] and inhibiting β-amyloid deposition.[77] Fish is a rich source of long-chain n-3 fatty acids, which have been shown to reduce oxidative damage and increase synaptic proteins and dendritic spine density.[77] There are potential ways to enhance propolis' cognitive benefits, including its ability to reduce inflammation, protect the brain from beta-amyloid toxicity and oxidative stress, and boost the production of brain-derived neurotrophic factor.[78] Propolis is believed to reduce cholesterol by inhibiting hydroxymethylglutaryl-CoA (HMG-CoA reductase).[79]

# 6 | STRENGTHS AND LIMITATIONS

Strengths: (a) this study is the first investigation that will be designed to evaluate the effect of MIND diet and Propolis supplementation on MetS indices among MetS subjects. Randomized control trial; (b) including large sample size; (c) controlling the confounder factors such as baseline, gender, education, surgery, drug, supplementation, physical activity, age, hospitalization, and food intake; (d) blood sampling and measuring biochemical parameters in the laboratory of the same Health Center where the participants will be 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 considerable effects on our results.

## AUTHOR CONTRIBUTIONS

**Zainab Gholami**: Conceptualization; software; investigation; writing—original draft; methodology; data curation; resources; writing—review and editing; visualization; formal analysis. **Mohammad Reza Maracy**: Formal analysis. **Zamzam Paknahad**: Conceptualization; funding acquisition; project administration; supervision; writing—review and editing.

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

Zamzam Paknahad 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.

The present article does not encompass any aspect of data sharing as it does not involve the generation or analysis of data sets.

The questionnaires are available in Persian upon request.

## ETHICS 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 will be obtained from all the participants.

## TRANSPARENCY STATEMENT

The lead author Zamzam Paknahad affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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