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A Holistic Approach to Improve Metabolic Health: A Practical Review

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Abstract

Metabolic syndrome (MetS) poses a significant health risk in developed countries like the United States, linked to poor diet, inactivity, aging, and genetic factors. It increases the likelihood of serious health issues, such as atherosclerotic cardiovascular disease (ASCVD), type 2 diabetes (T2DM), and cognitive impairment.

Preventing MetS is vital; this review focuses on natural methods to improve health by enhancing gut health, adopting healthier dietary choices, and incorporating functional foods, supplements, and herbs. These practical and cost-effective approaches target individuals without underlying endocrine disorders, emphasizing the importance of proactive health management.

Keywords: Metabolic Syndrome (MetS), Alternative Therapies, Natural Remedies, Metabolic Health, Obesity, Weight Management

Introduction

The Metabolic syndrome (MetS) is a cluster of metabolic disorders that includes high blood pressure, obesity, excess body fat around the waist, impairments in protein, glucose, lipids, and carbohydrates, and a higher risk of type 2 diabetes mellitus (T2DM), atherosclerotic cardiovascular disease (ASCVD), and cognitive impairment. (1–4) In the 2009-2010 NHNES survey, 22% of women and 24% of men had MetS. (4) The most prescribed medications for individuals with MetS include beta-blockers, statins, fibrates, and Glibenclamide. However, these medications are frequently expensive, have a poor patient tolerance rate, are linked to several adverse side effects, and lack long-term efficacy. (1) Therefore, prevention is the most effective strategy for addressing MetS.

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Holistic Approach

MetS is nutritionally dependent and takes a holistic approach to address metabolic health. It is assumed that these patients do not have any other underlying endocrine disorders, such as adrenal, thyroid, or sex hormone imbalances.

Improve Gut Health

Gut health is crucial for overall health, as it plays a significant role in 70% of immune function, including inflammation modulation, defense against pathogens, hormone balance, vitamin production, nervous system modulation, energy production, acid/alkaline balance, fluid and electrolyte balance, toxin and xenobiotic elimination, and neurotransmitter production. (5–8) **Xenobiotic** refers to any chemical

substance that is not naturally produced or expected to be in the body. (9) This includes things like compounds from plants, medications, pesticides, cosmetics, artificial flavorings and fragrances, food additives, industrial chemicals, and environmental pollutants. (9)

Avoiding Environmental Toxins

The risk of metabolic dysfunction is increased by environmental contaminants, especially endocrine-disrupting compounds (EDCs), which are exogenous substances or mixtures of chemicals that interfere with any component of hormone action. (10–12) However, this toxicity can be reduced by making dietary and lifestyle modifications, such as choosing organic food sources, avoiding microwaving and using plastic containers, and checking ingredient lists before purchasing products. (10,11) According to the Endocrine Society, research on EDCs is expanding, so keep an eye out for updates on goods that can improve your family's health. (12) Use the resources below to learn more: Pediatric Environmental Health Toolkit: psr.org/resources/pediatric-toolkit.html; (12) Environmental Working Group: ewg.org; (12) National Institute of Environmental Health Science: niehs.nih.gov. (12)

Below are brief descriptions of pathways that some functional foods and supplements modulate to achieve health benefits:

AMP-activated protein kinase (AMPK) serves as an energy gauge for our cells, enabling them to manage their energy utilization effectively. (13) When our body senses a lack of nutrients, AMPK activates to enhance the uptake of glucose and the burning of fats for energy; in contrast, when needed, it slows down processes that use energy, such as creating new glucose and fats, helping to bring everything back into balance. (13)

Peroxisome proliferator-activated receptor-γ coactivator (PGC-1α) is a crucial protein that regulates the body's energy utilization. (14) It's especially activated when we're exposed to cold temperatures. (14) PGC-1α collaborates with multiple proteins to regulate functions such as burning lipid and glucose, generating new mitochondria, and other essential processes that maintain our health. (14)

Sirtuin-1 (SIRT1) is a key protein that helps our body manage energy, especially when we're eating less. (15) When active, SIRT1 helps maintain steady blood sugar levels and ensures our body uses energy more efficiently. (15) SIRT1 plays a significant role in how the body handles fat—specifically, how it's stored and utilized—which is crucial for maintaining a healthy weight. (15)

Studies show that SIRT1 helps the liver with metabolism, supports the breakdown of fat, and even facilitates the conversion of regular white fat into a more active type of fat (like brown fat) that burns more energy. (16)

Additionally, SIRT1 helps regulate the amount of insulin the body produces, responds to hunger signals in the brain, reduces inflammation associated with obesity, and maintains the body's internal clock in sync with its metabolic processes. (16)

Tumor Necrosis Factor-alpha (TNF-α) is a pro-inflammatory cytokine produced by the body that plays a key role in inflammation and various metabolic activities and is especially important in how our body metabolizes lipids. (17) Research has shown that individuals who are obese or have MetS tend to have higher levels of TNF-α, and lowering chronic inflammation and TNF-α levels may help reduce the risk of cancer. (18,19)

Insulin-like Growth Factor-1 (IGF-1) is like insulin, but it has its own essential jobs in the body. (19) It helps build proteins, utilizes fat for energy, and influences the production of growth hormone and insulin in the body. (19)

In people with type 1 diabetes (T1DM), the body doesn't make enough IGF-1. In T2DM, IGF-1 doesn't work correctly. (19) Studies have shown that administering IGF-1 can help lower blood sugar levels and enhance the body's response to insulin in both types of diabetes. (19)

Food as Medicine

Some have suggested that the Mediterranean diet or lifestyle is the healthiest. (10,20,21) Fiber, antioxidants, protein, and moderate fat levels, primarily from monounsaturated (MUFA) and omega-3 polyunsaturated fatty acids (PUFA), as well as regular physical activity, contribute to its health benefits. (10,20,21) The most extensive study of Mediterranean diet, PRDIMED, a 4.8-year observational study in Spain, included 7,447 participants (55 to 80 years of age, 57% women) with a high risk for heart disease, divided into three groups: Mediterranean diet with added extra-olive oil, Mediterranean diet with added nuts, and low-fat diet as the control group: the result demonstrated the incidence of cardiovascular events was lower among those assigned to a Mediterranean diet supplemented with extra-virgin olive oil or nuts than among those assigned to

low-fat diet. (22) Furthermore, the Mediterranean diet supplemented with extra-virgin oil or nuts showed a combined 31% and 28% reduced risk of heart attack, stroke, and death from heart disease, respectively. (23) Additionally, 13.7% of individuals with MetS were able to reverse their condition. (23) As per the PRDIMED authors, compared to the control diet, the hazard ratio for a Mediterranean diet with nuts was 0.72 (95% CI, 0.54 to 0.95) and for a Mediterranean diet with extra-virgin olive oil was 0.69 (95% CI, 0.53 to 0.91) in the intention-to-treat analysis that included all participants and adjusted for baseline characteristics and propensity scores. (23) The results were comparable after removing 1588 participants who were known or suspected to have deviated from the protocol. (23)

The new Dietary Guidelines for Americans 2020–2025, released in 2020, support the Mediterranean diet lifestyle, emphasizing the significance of eating whole food and recommending that more than half of every meal's portion should be vegetables and fruits, which are beneficial for gut health and lipid management. (24) However, the Dietary Guidelines for Americans 2020–2025 were written for professional audiences; hence, a consumer-friendly version of the guidelines was created: MyPlate.gov (https://www.myplate.gov/), an official site that provides easy, low-cost recipes, meal planning, and a wealth of health information for consumers. (25) An individual can set a personal goal for healthy eating or personalize a "plate" for every meal by selecting from the five food groups: fruits, vegetables, grains, protein foods, and dairy, based on personal and cultural preferences and choices. (25) Additionally, you can download the MyPlate app on your smartphone for all its functions. Advanced meal planning can make dietary changes easier by using a device application, such as a computer or smartphone.

Functional foods deserve special attention because they have the potential to modulate glucose metabolism and reduce inflammation, which would help manage MetS and promote metabolic health. (26) It has been demonstrated that consuming three meals daily for four weeks with an antioxidant-rich diet, including polyphenols, flavonoids, vitamins A, C, D, and E, lipoid acid, minerals, omega-3, as well as fiber, can lower oxidative stress, enhance metabolic profiles, and decrease central obesity, dyslipidemia, and arterial stiffness. (26–28) Table 1 provides a summary of the evidence and clinical applications of functional foods, all of which have level 1 evidence. The evidence grade is based on Melnyk & Fineout-Overholt's 2023 levels of evidence. The 2020–2025 American Dietary Guidelines and MyPlate.gov recommend both chia seeds and flaxseeds as part of a daily intake of plant-based protein sources, alongside options such as salmon and other fatty fish for seafood, and kale for vegetables. (24,29) Therefore, for daily intake recommendations of chia seeds, flax seeds, salmon, and kale, use MyPlate, either the web version or the app, to personalize the portion of each food group you eat with every meal by incorporating chia seeds, flaxseeds, salmon, and other fatty fish, as well as kale, into your daily meals. Turmeric root has an excellent quality of meta-analysis and three review papers supporting its efficacy. Green tea also has a high quality of meta-analysis and several RCTs backing its clinical application. In Column one of Table 1, beside the name of functional food, you will also see common side effects (SE) of each, and recommended dosage of turmeric roots and green tea, since these two are not found on the MyPlate website or app.

Noteworthy regarding Omega-3 fatty acids

Traditionally, omega-3 supplementation is held preoperatively for the concerns of bleeding, however, growing evidence from randomized controlled studies has suggested the biochemical antiplatelet effect of fish oil does not translate into increased bleeding risk during or after surgery, citing the result of the OPERA, an RCT of 1516 participants from 28 health centers from United States, Italy, and Argentina, published on American Heart Association Journal, the study found that there was no difference in any of the bleeding outcomes between fish oil and the placebo groups. (62,63) Another review analyzing eight clinical studies including over 600 subjects support safe consumption of fish oil even at a short-term doses up to 10 g/day EPA+DHA or consumed for up to 52 weeks above 1.5 g/day in selected vulnerable and sensitive populations such as patients with gastrointestinal cancer or patients in an ICU, the authors found no evidence to support any concern to raise the risk for occurrence of increasing bleeding with consuming fish oil. (64) We recommend that readers exercise caution with these new findings and consult their healthcare practitioners thoroughly to make informed decisions based on their unique individual circumstances.

Supplements and Herbs

Food is the best medicine. However, when necessary, we utilize supplements or herbs to fulfill our

nutritional requirements. Table 2 provides a summary of supplements and herbs, including their metabolic effects, main clinical findings, applications, and relevant references. These have been selected for their high efficacy in combating MetS; they have either evidence level 1 or 2 ratings, in addition to being low-cost and accessible. In Table 2, Column 1 contains the supplements' names, dosages, and common SE. Column 2 provides the Metabolic effect, and column 3 indicates the main clinical findings and evidence grade based on Melnyk & Fineout-Overholt's 2023 levels of evidence. Lastly, column 4 provides references.

Conclusions

This review presents a comprehensive and effective approach to addressing MetS by focusing on the four pillars: enhancing gut health and the microbiome, reducing exposure to environmental toxins, improving insulin sensitivity, decreasing inflammation, and increasing basal metabolic rate. It is essential to acknowledge that regular physical activity plays a crucial role in managing MetS and promoting overall well-being.

When considering dietary strategies, prioritizing nutrient-rich foods is essential due to their substantial health benefits. The Mediterranean diet emerges as a particularly effective option, supported by robust clinical evidence demonstrating a reduced risk of developing MetS. Functional foods—rich in polyphenols, vitamins, and minerals—act as powerful antioxidants, support the gut microbiome, and improve metabolic function. Key components of the Mediterranean diet and functional foods, including fiber, protein, monounsaturated fatty acids (MUFAs), and omega-3 polyunsaturated fatty acids (PUFAs), contribute to its beneficial effects.

The Dietary Guidelines for Americans (2020-2025) align with these recommendations, promoting the Mediterranean diet and emphasizing the consumption of whole foods, with a recommendation that more than half of each meal consist of vegetables and fruits. Four out of the six functional foods highlighted in this review are also included in these guidelines. The MyPlate.gov website and app (the consumer version of the Dietary Guidelines) provide user-friendly resources to help individuals incorporate these recommendations into their daily routines.

Planning meals using tools like the MyPlate website or app can help integrate these evidence-based recommendations into daily life. The following functional foods, supported by strong scientific evidence, are especially beneficial:

1. **Chia Seeds:**
   Level 1 evidence. Recommended by the Dietary Guidelines for Americans (2020–2025) and MyPlate.gov as a plant-based protein source. Chia seeds are rich in fiber and omega-3 fatty acids, which support gut health, enhance insulin sensitivity, reduce inflammation, and stimulate metabolic activity.
2. **Flaxseeds:**
   Level 1 evidence. Also recommended by the Dietary Guidelines for Americans (2020–2025) and MyPlate.gov as a plant-based protein source. Flaxseeds help lower glucose, insulin, and lipid levels, improve insulin sensitivity, and provide anti-inflammatory and antioxidant benefits, aiding in weight management.
3. **Salmon and other Fatty Fish:**
   Level 1 evidence. Recommended as a seafood protein source by the Dietary Guidelines for Americans (2020–2025) and MyPlate.gov. Fatty fish and omega-3 supplementation act as potent antioxidants and anti-inflammatories, reducing waist circumference and glucose levels while supporting gut health.
4. **Turmeric Root:**
   Level 1 evidence. Supported by multiple meta-analyses and review papers. The active compound, curcumin, is recognized for its ability to suppress appetite, decrease glucose and insulin resistance, and provide both antioxidant and anti-inflammatory effects, thus promoting gut health and supporting weight management.
5. **Green Tea:**
   Level 1 evidence. Backed by high-quality meta-analyses and several randomized controlled trials. Green tea is noted for its antioxidant and anti-inflammatory properties and has been shown to increase basal metabolic rate and support metabolic health.
6. **Kale:**
   Level 1 evidence. Recommended as a vegetable source by the Dietary Guidelines for Americans (2020–2025) and MyPlate.gov. Kale is instrumental in promoting gut health, regulating glucose levels, and providing a rich source of antioxidants and anti-inflammatory compounds.

   Notably, it is essential to reevaluate traditional recommendations regarding omega-3 fish oil supplements, particularly in the context of presurgical periods. Recent research suggests a critical need for revised guidelines. Consultation with a healthcare provider is recommended to ascertain the most suitable approaches tailored to individual health needs.

Moreover, specific supplements and herbal agents may play a vital role in supporting overall health. Based on comprehensive research regarding efficacy, cost-effectiveness, and accessibility, we propose the following seven supplementary agents:

1. **Probiotics**

   Level 1 evidence. With validation from two high-quality meta-analyses and two randomized controlled trials, probiotics have been shown to improve gut microbiome diversity, enhance insulin sensitivity, lower A1C levels, and aid in weight reduction.

2. **Magnesium**

   Level 1 evidence. One high-quality meta-analysis and one RCT demonstrate that magnesium reduces fasting plasma glucose and insulin levels. It also improves insulin responsiveness, elevates HDL cholesterol levels, and contributes to improved mental health in individuals with diabetes.

3. **Vitamin D3**

   Level 2 evidence. Evidence from one RCT and one large cohort study suggests that sufficient vitamin D3 levels can reduce the risk of metabolic syndrome, particularly in older adults, individuals with excess body weight, and postmenopausal women.

4. **Selenium**

   Level 1 evidence. Two high-quality meta-analyses and one RCT support the efficacy of selenium in decreasing insulin levels and HOMA-IR, while also increasing HDL cholesterol.

5. **Coenzyme Q10 (CoQ10)**

   Level 1 evidence. Two high-quality meta-analyses and one RCT back CoQ10. As a potent antioxidant and anti-inflammatory compound, it plays a crucial role in regulating glucose metabolism, breaking down triglycerides, protecting the liver, and producing cellular energy (ATP). When used in conjunction with selenium, its antioxidant capacity is further amplified through a synergistic interaction.

6. **Berberine**

   Level 1 evidence. Berberine, validated by one high-quality meta-analysis and three systematic reviews, has gained recognition as an effective botanical compound for improving metabolic parameters. It helps regulate blood glucose and lipid concentrations, positioning it as a potential alternative to statins and metformin. Berberine also influences gut microbiota composition and exhibits significant anti-inflammatory activity, thereby contributing to enhanced metabolic resilience.

7. **Resveratrol (RSV)**

   Level 1 evidence. Resveratrol, substantiated by one high-quality meta-analysis and one randomized controlled trial, is a potent antioxidant and anti-inflammatory agent. It enhances insulin sensitivity and facilitates weight reduction, making it especially beneficial in addressing insulin resistance and related metabolic disturbances.

Incorporating these dietary components and supplements into an individual's regimen may serve as a comprehensive strategy to prevent MetS and optimize overall health outcomes.

Declaration of Non-conflict of Interest
The authors have no conflict of interest in preparing this manuscript. This study received no specific grant from public, commercial, or not-for-profit agencies.

Table 1. Functional food: Evidence Summary and Clinical Applications

Functional Food: **Dosage/Common Side effects (SE)**	**Evidence Grade/ Summary**	**Clinical Applications**
Chia Seeds: **Dosage:** use MyPlate (website or app) to personalize. For its fiber content, according to Mohd Ali et al. (2012), chia seeds contain 34-40 g of dietary fiber per 100 g, which is 100% of the recommended daily intake for adults. (30) **SE:** GI symptoms such as bloating, gas, cramping or constipation may occur if not taking with enough water due to its high content of fiber. (31) Avoid during IBS acute flare-up. (32)	Level 1/ Omega-3 contents in Chia seeds decreased triglycerides and LDL in addition to BP, hence, providing cardioprotection and lower the risk of diabetes and cardiovascular disease. (30,33,34) The action of insoluble fiber, which is helpful for blood sugar regulation, minimizing constipation, maintaining a healthy GI tract, and lowering cholesterol and cancer-causing substances, makes it advantageous for metabolic stimulation and cardioprotection. (34) Quercetin and caffeic acid are primarily responsible for the antioxidant properties of chia seeds. (33,34)	• Regulate Glucose • Minimize constipation • Improve Gut Health • Improve Lipids • Prevent cancer • Boost metabolism • Cardioprotection • Antioxidant • Prevent Diabetes • Prevent CVD
Flaxseeds **Dosage:** use MyPlate (website or app) to personalize. **SE:** GI symptoms such as bloating, gas, cramping or constipation if not taking with enough water due to its high content of fiber. (31) Avoid during IBS acute flare-up. (32)	Level 1/Flaxseeds possess cardioprotective properties, lower blood pressure values, and exhibit anti-inflammatory and antioxidant effects. (35,36) Flaxseeds can help reduce blood sugar in T2DM. (35,36) In addition, due to a phytoestrogenic impact, they can be protective against breast cancer. (21,35,37) Flaxseed may be advantageous for weight loss, as it reduces insulin concentration, triglycerides (TG), high-sensitivity C-reactive protein (hs-CRP), and leptin, thereby enhancing insulin sensitivity and increasing high-density lipoprotein (HDL) levels. (37)	• Anti-inflammatory • Antioxidant • Cardioprotective • Reduce blood sugar • Reduce insulin • Improve insulin sensitivity • Phytoestrogenic • Weight loss • Improve lipids
Salmon and other fatty fish/ Omega-3 fatty acid **Dosage:** use MyPlate (website or app) to personalize. **SE:** See special note below.	Level 1/ They have anti-inflammatory and antioxidant properties, may reduce the risk of heart disease, improve lipids, and have neuroprotective properties against multiple sclerosis, depression, and Alzheimer's disease. (21,38,39). Furthermore, it has been shown to enhance intestinal flora. (40) In a study of omega-3 fatty acid supplementation, significant decreases in waistline, TG, fasting blood glucose (FBG), HOMA-IR, and high-sensitivity C-reactive protein (hs-CRP) were linked to omega-3 fatty acids alone. (41)	• Anti-inflammatory • Antioxidant • Cardioprotective • Improve lipids • Neuroprotective • Improve gut health • Decrease fasting glucose • Decrease waistline

Turmeric root **Dosage:** Adding it to the food as a spice, according to the WHO, the acceptable daily intake (ADI) for curcumin is 1.4 mg per pound (or 0–3 mg per kilogram) of body weight. (42) **SE:** In some cases, patients may experience occasional gastrointestinal side effects, such as nausea and diarrhea. (43–45)	Level 1/ A meta-analysis by Akbari et al. (2019) found curcumin significant reduced BMI, weight and waist- circumference (WC) levels as well as decreasing leptin level while increasing adiponectin level. (4) Curcumin is proven to increases glutathione concentration and regulate inflammatory cytokines, suggesting a potential role in preventing endothelial dysfunction. (33) Curcumin increases adiponectin while reducing leptin level in MetS patients in a RCT by Panahi et al. (2016) (46) In another study by Panahi et al. (2017), supplementation of curcumin significantly increased total antioxidant capacity (TAC) ($p<0.001$) and reduced superoxide dismutase (SOD) activity ($p<0.001$) in patients with T2DM. (47) Momtazi et al. (2016) examined curcumin's role as a microRNAs epigenetic modulators, which further supported its effects in anti-inflammatory, antioxidant, and disease prevention in non-cancer diseases. (48) Cox et al. (2022) found reported that curcumin has been used for antiviral, antibacterial, anti-cancer for ages in traditional medicines; furthermore, it exerts CVD protection by upregulating SIRT1 and modulating other pathways to decrease aging related inflammation. (49)	• Weigt loss • WC reduction • Regulate appetite • Hepatoprotective • Anti-inflammatory • Anticancer • Regulate glucose • Improve insulin resistance • Antioxidant • Prevent CVD • Antiviral • Antibacterial

Green tea **Dosage:** Hu et al. (2018) found that brewed green tea contains an average of 126.6 mg of total catechins and 77.8 mg of EGCG per 100 mL, as consumed, based on a 1 g leaf/100 mL infusion. (50) A daily intake of 704 mg of EGCG from GTEs in beverage form is considered safe for adults. (50) Generally, there is no safety concern when consuming green tea for healthy adults. (51) **SE:** Green tea can cause insomnia, irritability, increased heart rate, and higher blood pressure due to its caffeine content. (51) Other common side effects are nausea, constipation, gastrointestinal discomfort, and increased urination. Caffeine intake is advisable to avoid during pregnancy and lactation. (51)	Level 1/ Green tea exhibits anti-inflammatory and antioxidant properties, promoting autophagy and enhancing metabolism through increased fat oxidation. (52) This agent also reduces triglycerides (TG), decreases the risk of cardiovascular disease, and exhibits anti-cancer properties. (53–57) Green tea modulates cell signaling, including the SIRT1 pathway, which activates the AMPK and PGC1-α pathways, thereby affecting gene expression related to mitochondrial efficiency and fat oxidation. (52,57,58) De Oliveira et al. (2024) conducted a meta-analysis, include 12 randomized controlled trials (RCTs), have demonstrated that daily doses of 100–800 mg of green tea extracts (GTEs) containing epigallocatechin gallate (EGCG) significantly decrease serum TNF-α levels, thereby exerting potent anti-inflammatory and cancer-protective effects. (59)	• Anti-inflammatory • Antioxidant • Promote autophagy • Enhance metabolism • Mild stimulant • Increase fat burning • Weight loss • Improve lipids • Prevent CVD • Prevent cancer
Kale **Dosage:** use MyPlate (website or app) to personalize. **SE:** General safe; however, due to its high potassium and vitamin K content, individuals who are on beta blocker, blood thinner (e.g. coumadin), and has kidney disease should consume it in moderation.	Level 1/ In a review by Oretega-Hernandez et al. (2021), kale was found to decrease LDL, triglyceride, improve BP and glucose, in addition to its anti-inflammatory effects by reducing TNFs and IL-1β. (60) Moreover, the authors reported kale has the ability to prevent varies chronic diseases: cancer, CVD, T2DM, and inflammatory related through multiple signaling pathways including MAPK and others. (60) Satheesh in his review article (2020) found kale had another therapeutic property: improving gut microbiome. (61)	• Antioxidant • Improve lipids • Anti-inflammatory • Regulate BP • Improve glucose • Prevent cancer • Prevent CVD • Prevent T2DM • Improve gut health

Table 2. Supplements and Herbs: Evidence Summary and Clinical Applications

Supplement/Herbs **Dosage/Common SE**	**Metabolic Effect**	**Evidence Grade/Main Clinical finings**	**References**
Probiotics **Dosage:** Infancy-related probiotic dosage ranged from 2×10^6 to 6×10^9 CFU/day for 2 to 24 weeks; further research is required to determine the appropriate dosage and duration for this age group beyond a 24-week therapy duration. (65–67) There is no consensus on adult dosages; clinical trials have used doses ranging from 10^5 to 10^{15} CFU/day without adverse side effects being noted. (65,66) **SE:** Probiotics are generally considered safe; common side effects include gastrointestinal discomfort, nausea, diarrhea, constipation, and bloating. (66,67)	Alter the gut microbiota, improve insulin sensitivity, lower HbA1c levels, modify lipid profiles, and reduce oxidative stress.	Level 1/A meta-analysis by Yao et al. (2017) demonstrated that probiotic supplementation was associated with improved HbA1C and fasting insulin levels in T2DM patients across 12 RCT studies, involving 684 patients. (68) Kassain et al. (2018) conducted a double-blind, placebo-controlled, randomized, parallel-group clinical trial involving 120 adults, with findings indicating a significant decrease in the prevalence of hypertension in the probiotic group (p=0.04) and hyperglycemia in both the probiotic and symbiotic groups (p=0.01 and 0.005, respectively). (69) Moreover, the prevalence of MetS substantially decreased in the probiotic group compared to the placebo group. (69)	(68,69)
	Reduce visceral fat and weight loss	In a 12-week clinical trial, 210 healthy adults with high visceral fat levels between the ages of 35 and 60 were randomly assigned to consume 200 g/day of fermented milk containing 10^7, 10^6, or 0 (control) CFU of *Lactobacillus gasseri* SBT2055 (LG2055) per gram of milk; participants who received 10^7, 10^6 CFU/g milk of *Lactobacillus gasseri* showed noticeable reductions in visceral fat area (mean reductions of 8.5% and 8.2%, respectively), BMI, waist and hip circumferences, and body fat mass. (66,70) Rasaei et al. (2024) conducted a more recent meta-analysis of 97 papers and discovered that probiotics reduced body weight and BMI. (65)	(65,66,70)

Magnesium **Dosage:** For individuals aged 9 and older, a daily intake of 240–420 mg of magnesium is recommended; for pregnant and lactating women, the suggested range is between 310 mg and 400 mg, depending on age. (71) **SE:** Magnesium from food typically poses no health concerns; however, magnesium toxicity can occur when a massive intake of magnesium-containing laxatives and antacids exceeds 5,000 mg per day. (71) **Interactions with Medications:** Mg-rich supplements can decrease the absorption of bisphosphonates, such as Fosamax, a medication used to treat osteoporosis, as well as antibiotics like tetracyclines (demeclocycline or doxycycline) and quinolone antibiotics (ciprofloxacin and levofloxacin). (71) These medications should be taken at least 2 hours apart from Mg-containing supplements. (71)	Reduction in fasting plasma glucose (FPG), boosting insulin sensitivity in DM patients.	Level 1/A meta-review by Veronese et al. (2021) analyzed 18 randomized controlled trials (RCTs), including 12 studies that involved individuals with diabetes and 16 trials that focused on those at high risk of developing the condition [participant total: placebo group (n=334), magnesium treatment (n=336)] found a reduction in fasting plasma glucose (FPG) levels (from nine studies; SMD=–0.40; 95% CI: –0.80 to 0.00; I^2=77%) in individuals with diabetes. (72) Among participants at high risk for diabetes (226 receiving magnesium and 227 on placebo), magnesium supplementation drastically enhanced plasma glucose levels following a 2-hour oral glucose tolerance test (three studies; SMD=−0.35; 95% CI: −0.62 to –0.07; I^2=0%) and indicated trend-level reductions in homeostasis model assessment-insulin resistance (HOMA-IR) (five studies; SMD=−0.57; 95% CI: −1.17 to 0.03; I^2=88%). (72)	(72)
	Decrease insulin level, increase HDL, decrease FPG while improving mental health in CHD and T2DM patients.	Hamedifard et al. (2020) Conducted a randomized, double-blind, placebo-controlled trial on 60 subjects suffering from coronary heart disease (CHD) and T2DM, results demonstrated supplementation of Mg and zin significantly decreased FPG (β− 9.44 mg/dL, 95% CI, −18.30 to −0.57; p=0.03) and insulin levels (β− 1.37 μIU/mL, 95% CI, −2.57 to −0.18; p=0.02). (73) Moreover, HDL levels were remarkably enhanced (β=2.09 mg/dL, 95% CI=0.05 to 4.13; p=0.04) compared to the placebo. (73)	(73)

Vitamin D3 Dosage: The recommended daily intake is 400 IU/day for children up to 12 months, 600 IU/day for those aged 1 to 70 years, and 800 IU/day for individuals 70 years and older. For pregnant and lactating women, the recommended intake is 600 IU/day. (74)	Decrease risk of developing obesity, hypertriglyceridemia, and MetS in elders.	Level 2/ An extensive cohort study conducted in Korea on 2,936 elderly individuals found that a low vitamin D3 level was associated with high waist circumference, hypertriglyceridemia, low HDL, and an increased risk of developing MetS. (76)	(76)
	Improve BP, insulin sensitivity, and FPG in overweight and obese children.	Rajakumar et al. (2020) implemented a randomized, double-masked, placebo-controlled trial involving 225 overweight and obese children aged 10 to 18 years, correcting vitamin D deficiency through vitamin D3 supplementation with 1000 or 2000 IU/day resulted in reductions in blood pressure (BP) and fasting glucose concentration, as well as improved insulin sensitivity. (77)	(77)
SE: Vitamin D toxicity is rare from food source, the Food and Nutritional Board established tolerable upper intake levels (ULs) for vitamin D daily intake: 0–6 months 1000 IU/day, 7–12 months 1500 IU/day, 1–3 years 1500 IU/day, 4–8 years 3000 IU/day, nine and older including pregnant and lactation women 4000 IU/day to avoid vitamin D toxicity from occurring. (74,75)	Significant reduction in TG, insulin, and HOMA-IR; also decrease risk of developing MetS in postmenopausal women.	Ferreira et al. (2020) conducted a randomized, double-masked, placebo-controlled study on 160 postmenopausal women aged 50–65 years: the group receiving D3 1000 IU/day for 9 months showed a significant reduction in TG (–12.2%, p=0.0001), insulin (–13.7%, p=0.008), and HOMA-IR (–17.9%, p=0.007). (78) In contrast, the placebo group showed a 6.2% increase in glucose levels (p=0.009). Analysis, adjusted for age, time since menopause, and BMI, showed that women supplemented with D3 had a lower risk of MetS (Odds ratio (OR) 0.42; 95% confidence interval (CI: 0.10 to 0.52) compared to the placebo group ($p<0.05$). (78)	(78)
Selenium **Dosage:** Daily recommended selenium intake for infant up to 6 months is 15 mcg/day, for 7–12 months, 20 mcg/day, for 1–3 years, 20 mcg/day, for 4–8 years, 30 mcg/day, for 9–13 years, 40 mcg/day, for 14 and older, 55 mcg/day, for pregnancy and lactation, 60 mcg/day and 70 mcg/day respectively. (79). **SE:** Toxicity may occur if Brazil nuts are consumed regularly in large amounts, or acute selenium toxicity results from ingesting poorly formulated over-the-counter products containing excessive amounts of selenium. (79)	Decrease risk of CVD, reduce insulin level and HOMA-IR, increase HDL.	Level 1/ From a meta-analysis of 16 RCTs by Zhang et al. (2016) showed selenium concentrations range from 55 to 145μg/L were associated with a notably lower risk of CVD and oral selenium supplements at median dose: 200μg/day for 2 weeks to 144 months significantly raised blood selenium concentrations by 56.4μg/L (95% CI: 40.9 to 72.0μg/L). (80) Quyang et al. (2022) reported in their meta-analysis that selenium supplementation considerably reduced serum insulin levels (SMD: –0.53; 95% CI: –0.84 to –0.21, p=0.001, I^2=68%) and HOMA-IR (SMD: –0.50, 95% CI: –0.86 to –0.14, p=0.006, I^2=75%) and increased high-density lipoprotein cholesterol (HDL-C) levels (SMD: 0.97; 95% CI: 0.26 to 1.68, p=0.007, I^2=92%). (81)	(80,81)

Coenzyme Q10 (CoQ10) **Dosage:** The typical daily dose for adults is 100–300 milligrams per day. (82,83) **SE:** CoQ10 is safe, even at the highest dose cited in the literature. However, gastrointestinal effects such as abdominal discomfort, nausea, vomiting, diarrhea, and anorexia have occurred. (84)	Antioxidant, part of ATP production, decrease TG and TC, enhance glucose control and liver function, anti-inflammatory, prevention of CVD.	Level 1/ CoQ10 is involved in the ATP production as a major component of the mitochondrial electron transport chain. (85,86) Results from a meta-analysis on 21 RCTs by Sharifi et al. (2018) showed that CoQ10 supplementation 100–200 mg/day significantly reduced serum TG levels (SMD –0.28; 95% CI: –0.56 to –0.005) and total cholesterol (TC) (SMD –0.07; 95% CI: –0.45 to 0.31) in patients with metabolic disorders. (85) Duldla et al. (2020) conducted another meta-analysis involving 6 RCTs and 318 participants indicated that CoQ10 supplementation enhanced glucose control and liver function in individuals with MetS while significantly reducing inflammation markers such as C-reactive protein (CRP) and interleukin (IL)-6 in comparison to those in the placebo group (SMD: –0.31 (95% CI: –0.54 to -0.08); I^2=51%, p=0.07). (87) Moreover, a systematic review of 12 studies by Dludla et al. (2020) demonstrated that CoQ10 supplementation lowers the risk of CVD in diabetic patients compared to the placebo group. (88)	(85–88)
	Selenium and CoQ10 have synergetic antioxidant function.	Alehagen et al. (2022) conducted a prospective, randomized, double-masked, placebo-controlled trial in Sweden, utilizing Structural Equation Modeling (SEM), to investigate the statistical interrelationships between inflammation-related biomarkers, oxidative stress, IGF-1, microRNA expression, fibrosis, and endothelial dysfunction, as well as their impact on clinical outcomes. (89) Either selenium yeast (200 μg/day) and CoQ10 (200 mg/day), or a placebo, was administered to 443 elderly community-living individuals for 48 months, followed by a 12-year follow-up. The authors concluded that supplementation with selenium and CoQ10 improved cardiac function and reduced cardiovascular mortality by decreasing both fibrosis (β=0.74; p<0.001) and myocardial scores (β=0.65; p<0.001), in addition to enhancing overall quality of life. (89)	(89)
Berberine **Dosage:** The recommended initial dosage is 500 mg daily, with a maximum of 1500 mg per day as tolerated, divided into 2–3 doses with meals. (90,91) **SE:** Potential side effects include gastrointestinal discomfort, constipation, bloating, diarrhea, and hypoglycemia if taken without food. (90)	Alternative for statins and metformin in treating T2DM, obesity and hyperlipidemia, regulate gut microbiome, antitumor, anti-inflammatory, improve insulin resistance, improve lipids, reduce HOMA-IR.	Level 1/ Berberine has been used for treating diabetes mellitus (DM) obesity, and hyperlipidemia for thousands of years in Chinese and Ayurvedic medicine as an alternative to statins and metformin. (91–94) It can regulate the gut microbiome. (91,92) Berberine improves metabolic imbalance and insulin resistance by blocking genes that produce fat, thereby increasing heat generation and oxygen consumption, accelerating fat and glucose metabolism by activating the AMPK pathway. (91–95) It improved cognitive impairment, lowered insulin resistance while reducing TG, total TC, and LDL according to Ye et al. (2021), a meta-analysis on 18 RCTs: HOMA-IR (SMD: 1.25; 95% CI: 0.25 to 2.24; *p*=0.01), FPG (SMD: 0.65; 95% CI: 0.28 to1.03; *p*=0.00), TG (SMD: 0.94; 95% CI: 0.49 to1.38; *p*=0.00), TC (SMD: 1.06; 95% CI: 0.64 to1.48; *p*=0.00), and LDL (SMD: 1.77; 95% CI: 1.11 to 2.44; *p*=0.00). (93)	(91–95)

Resveratrol (RSV) **Dosage:** The liposomal form of the Japanese knotweed is the best-known source for RSV. (45,96) The recommended dosage is 200–500 mg daily. (96,97) **SE:** RSV is possibly safe when taken in doses of up to 1500 mg for up to 3 months. (98) Higher doses, such as 2000–3000 mg daily for up to 6 months, have also been used safely; however, higher doses are more likely to cause gastrointestinal discomfort. (98)	Improve gut microbiota, lower glucose and A1C, anti-inflammatory, weight loss, reduce HOMA-IR, decrease TC, VLDL, FPG, insulin levels, and BP.	Level 1/ Cucu et al. (2021) found people who took RSV regularly, the composition and diversity of their gut microbiota altered significantly in a positively way. (96) RSV activates the AMPK pathway and SIRT1. (3,97) Zhou et al. (2022) conducted a meta-analysis on 25 RCTs including 1,171 participants demonstrating that RSV has a drastic impact on regulating lipid and glucose metabolism in obese and diabetic patients: waist circumference (SMD=–0.36; 95% CI: –0.59 to –0.14; p=0.002; I^2=88%), HbA1c (SMD=–0.48; CI: –0.69 to –0.27; p≤0.001; I^2=94%), TC (SMD=–0.15; CI: –0.3 to –0.01; p=0.003; I^2=94%), low density lipoprotein cholesterol (LDLC) (SMD=–0.42; CI: –0.57 to –0.27; p≤0.001; I^2=92%), high density lipoprotein cholesterol (HDLC) (SMD=0.16; CI: –0.31 to –0.02; p=0.03; I^2=81%)n following resveratrol administration. (97) According to Zhu et al. (2017), meta-analysis on 9 RCTs produced similar results: FPG (−0.29mmol/l, 95% CI:−0.51,−0.06, p<0.01) and insulin levels (−0.64 U/mL, 95% CI:−0.95,−0.32, p<0.0001) RSV also reduced HOMA-IR, systolic blood pressure, and diastolic blood pressure among participants with T2DM. (99)	(3,96,97,99)

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