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Integrative Medicine

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Vol. 21, Issue 10, October 2018
ReliasMedia.com

HEART DISEASE

ABSTRACT &COMMENTARY

Does a Gluten-free Diet Lower the Risk of Coronary Artery Disease in Adults?

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Dr. Corbette and Dr. Selfridge report no financial relationships relevant to this field of study.

SYNOPSIS: A prospective, cohort study of health professionals conducted over 24 years revealed no significant association between long-term consumption of gluten and the risk of coronary artery disease in both adult men and women with no history of coronary artery disease.

SOURCE: Lebwohl B, Cao Y, Zong G, et al. Long term gluten consumption in adults without celiac disease and risk of coronary heart disease: Prospective cohort study. *BMJ* 2017;357:j1892.

Gluten describes a family of storage proteins found largely in wheat, rye, and barley, consisting primarily of gliadin and glutenin. Gliadin is the main protein responsible for the pathology of celiac disease, an autoimmune disorder of the small bowel characterized by inflammation of the intestinal mucosa, villous atrophy, and hyperplasia of intestinal crypts triggered by exposure to dietary gluten.[1,2] The prevalence of celiac disease in the United States and Europe is about 1% and has risen over the last four decades.[1]

Celiac patients may experience symptoms of malabsorption, including diarrhea, weight loss, and nutrient deficiencies, but many only have minor gastrointestinal (GI) symptoms or none at all. In addition, persons who do not have celiac disease may experience GI and other symptoms associated with consumption of gluten, as well as symptom improvement with removal of gluten from their diets. Such individuals have non-celiac gluten sensitivity, a clinical diagnosis with an undetermined pathophysiology, no known biomarker, and a

Financial Disclosure: *Integrative Medicine Alert*'s Executive Editor David Kiefer, MD; Peer Reviewer Suhani Bora, MD; Relias Media Executive Editor Leslie Coplin; Editor Jonathan Springston; and Editorial Group Manager Terrey L. Hatcher report no financial relationships relevant to this field of study.

Integrative Medicine [ALERT]

Integrative Medicine Alert (ISSN 1096-942X) is published monthly by Relias Learning, 111 Corning Road, Suite 250, Cary, NC 27518-9238. Periodicals postage paid at Cary, NC, and additional mailing offices. POSTMASTER: Send address changes to *Integrative Medicine Alert*, Relias Learning, 111 Corning Road, Suite 250, Cary, NC 27518-9238.

GST Registration Number: R128870672.

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Summary Points

- Researchers followed health professionals from the Nurses' Health Study and the Health Professionals Follow-up Study with no prior history of coronary heart disease and used food-frequency questionnaires to determine their estimated gluten consumption over a period of 24 years.
- The primary outcome was coronary artery disease, determined by nonfatal or fatal myocardial infarction; 6,529 participants reported incident coronary artery disease during the study period.
- Several secondary analyses were performed, including adjustments for refined grains and whole grains. Overall gluten intake demonstrated no association with risk of coronary heart disease. However, when attributable to whole grain intake, there was a statistically significant inverse relationship between gluten intake and coronary heart disease.

worldwide prevalence reported to range from 0.6% to 6.0%.[1,3]

Coronary artery disease, also known as coronary heart disease (CHD) and ischemic heart disease, is one of the leading causes of morbidity and mortality in the United States. Celiac disease has been associated with an increased risk of CHD, a risk that is mitigated by a gluten-free diet in these patients.[1] To determine the potential effects of gluten on cardiovascular health in individuals without celiac disease, Lebwohl et al examined the association between estimated long-term gluten intake and the development of incident coronary artery disease.

Data were analyzed from 110,017 participants, including 64,714 women from the Nurses' Health Study (NHS) and 45,303 men from the Health Professionals Follow-up Study (HPFS). The NHS was initiated in 1976 with 121,700 female nurses, ages 30-55 years. The HPFS was implemented in 1986 to complement the NHS and included 51,529 male health professionals. Both studies were prospective and longitudinal in design, with an objective of investigating major risk factors for chronic disease development using data from questionnaires on various health practices and lifestyle habits.

Exclusion criteria for analysis in this study included: implausible reported daily energy intake (< 600 or > 3,500 kcal/day for women and < 800 or > 4,200 kcal/day for men); questionnaires missing gluten data; or a previous diagnosis of myocardial infarction (MI), angina, stroke, coronary artery bypass graft surgery, and cancer. In 2014, a history of celiac disease was solicited from participants; any individuals with a diagnosis of celiac disease were excluded from data analysis. If a participant developed a significant illness during the study period, such as diabetes, cardiovascular disease, or cancer, data for that individual were suspended assuming that significant illness might dramatically affect dietary composition. In these instances, the cumulative dietary gluten before onset of illness was used for analysis until the end of follow-up.

The two cohorts were evaluated using a 136-item, validated, semiquantitative food-frequency questionnaire, initially administered in 1986 and readministered every four years (1990, 1994, 1998, 2002, 2006, and 2010). Investigators used the Harvard T.H. Chan School of Public Health nutrient database, which is updated every two to four years, to calculate major nutrients consumed in the participants' diets. The quantity of gluten consumed was calculated from the protein content in the wheat, rye, and barley products reported in the participants' food questionnaires, based on recipe ingredient lists and using a conservative estimate of the gluten proportion of the protein at 75%. Coronary artery disease, the primary outcome of the study, consisted of fatal or nonfatal MIs. Fatal outcomes were confirmed by medical or autopsy records or as stated on the death certificate. Nonfatal events were self-reported by patients. If there was no history of CHD, but it was listed as the underlying cause of death, the outcome was termed probable myocardial infarction

Table 1: Dietary Gluten Intake and Coronary Heart Disease

Variables Considered in Secondary and Post Hoc Analyses

- Consumption of whole grains vs. refined grains
- Participant age (< 65 years vs. ≥ 65 years)
- Body mass index (< 25 kg/m^2 vs. ≥ 25 kg/m^2)
- Physical activity (< 18 MET hours vs. ≥ 18 MET hours/week)
- Smoking status (current vs. never vs. past)
- Aspirin and nonsteroidal anti-inflammatory use
- Family history of myocardial infarction
- Statin use
- History of hypertension
- Nonfatal vs. fatal myocardial infarction
- Dietary covariates (e.g., alcohol, red meat, trans fats, fruits, and vegetables)

and was considered together with the primary outcome as fatal MI.

Testing the hypothesis that greater amounts of dietary gluten are associated with an increased risk of CHD as indicated by acute nonfatal and fatal MI, participants were followed from 1986 until development of acute MI, death, or end of follow-up (June 2012 for NHS and January 2012 for HPFS). Participants were divided into quintiles of estimated gluten consumption based on the energy-adjusted grams of gluten per day. Cumulative average estimated gluten consumption was calculated and treated as a time variable. The authors conducted several secondary and post hoc analyses, taking into consideration the variables indicated in Table 1. The mean estimated daily gluten intake at baseline was 7.5 g (standard deviation [SD], 1.4) for women and 10.0 g (SD, 2.0) for men in the highest quintile, and 2.6 g (SD, 0.6) for women and 3.3 g (SD, 0.8) for men in the lowest quintile.

During the study period, 6,529 participants (2,431 women and 4,098 men) were reported to develop coronary artery disease, as indicated by acute MI. Of these, fatal MI was reported in 2,286 participants (540 women and 1,746 men).

Participants in the lowest quintile of gluten intake had a CHD incidence rate of 352 per 100,000-person years, while participants in the highest quintile of gluten intake had a CHD incidence rate of 277 per 100,000-person years, yielding an unadjusted rate difference of 75 (95% confidence interval [CI], 51-98) fewer cases per 100,000-person years between the upper and lower quintiles. However, after adjustments for non-dietary and dietary covariates, there was no association when comparing upper and lower quintiles of gluten intake (HR, 0.95; 95% CI, 0.88-1.02; *P* for trend = 0.29). The authors performed a secondary analysis specifically to adjust for gluten consumption from whole grains and refined grains. Adjusting for refined grains, so that all the variance in gluten intake was attributable to dietary whole grains, resulted in an inverse relationship between estimated gluten intake and the development of CHD (HR, 0.85; 95% CI, 0.77-0.93; *P* for trend = 0.002). However, adjusting for whole grains, so that all the variance in gluten intake was attributable to dietary refined grains, resulted in no association between estimated gluten intake and incident CHD (HR, 1.00; 95% CI, 0.92-1.09; *P* for trend = 0.77). Thus, higher levels of gluten consumption were associated with increased incident CHD only if the source of dietary gluten was from refined grain products.

■ COMMENTARY

According to the Centers for Disease Control and Prevention (CDC), heart disease is the leading cause of mortality in both men and women, with CHD being the most common pathology.[4] Approximately 370,000 deaths per year have been reported, along with more than 700,000 cases of MI.[5] There are many known risk factors for CHD, including hypertension, diabetes, smoking, and obesity. In recent years, the popularity of gluten-free diets among individuals without celiac disease has increased, possibly because the known high glycemic index of many gluten-containing foods contributes to insulin resistance or recent recognition of gliadin's proinflammatory properties, even in patients without celiac disease.[6] Certainly, social media and consumer product marketing have promoted these diets from a variety of angles, for better or worse.

There is limited evidence about the effect of gluten-free diets on overall cardiovascular health, although there is sufficient evidence that inclusion of whole grains in the diet has beneficial effects on health, including reduction in risk for CHD and type 2 diabetes.[7] These authors concluded there is no significant association with long-term gluten intake and the risk of developing incident CHD in patients without a prior history of CHD. The authors supported the current literature by showing a decrease in CHD risk with higher levels of gluten intake when the gluten intake was attributable to dietary whole grains, a positive effect likely due to soluble and insoluble fiber.

Although this study benefitted from a large sample size and long-term follow-up using repeated assessments, methodologic limitations should be considered. The study population was comprised of health professionals only, a potential selection bias prohibiting generalization of results to a more representative population, since health professionals may be more cognizant of evolving risk factors related to heart disease and may adjust health and lifestyle habits accordingly. In addition, participants with chronic disease diagnoses such as diabetes were not included in the analyses, again limiting

generalization of the results to a more representative population. The investigators attempted to control for many covariates associated with heart disease risk in their analyses, but could not possibly control for all known and unknown health habits conferring possible benefit. Recall bias is another potential confounder in this study, since dietary questionnaires asking for detail on estimated frequency and type of food intake and characteristic portion sizes consumed over the previous year were distributed only every four years. Although patients with celiac disease were excluded from the analysis, patients with non-celiac gluten sensitivity were neither identified nor excluded. Since the latter condition is at least as common as celiac disease, and implies a robust immunologically based inflammatory reaction to gluten, it would make sense to treat. Also, it is unknown who might have gluten reactions beyond celiac disease; this was not assessed, with no screening for non-celiac gluten sensitivity.

Physicians may find themselves fielding questions about gluten-free diets from patients without celiac disease or documented gluten sensitivity. This study fails to support any notion that gluten consumption is associated with an increased risk of CHD. Further, this study supports what other research has concluded: Consumption of whole grains is a "good thing" in that it is independently associated with a decreased risk of coronary disease. Additional research would be beneficial, assessing a more diverse study population and potentially employing digital technology and devices to assist with real-time dietary data monitoring in longitudinal studies. In the meantime, physicians can inform patients who do not have celiac disease or symptomatic gluten sensitivity that limiting dietary gluten intake does not provide any reduced risk of coronary disease and may interfere with a desirable and health-promoting intake of whole grains. ■

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MORTALITY

ABSTRACT & COMMENTARY

Coffee Consumption and Mortality

By Allison Becker, ND, LAc

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Dr. Becker reports no financial relationships relevant to this field of study.

SYNOPSIS: After rigorous evaluation using multiple statistics, an inverse relationship between coffee intake and all-cause mortality was demonstrated consistently across the racial/ethnic groups examined.

SOURCES: Gullar E, Blasco-Colmenares E, Arking DE, Zhao D. Moderate coffee intake can be part of a healthy diet. *Ann Intern Med* 2017;167:283-284.

Park SY, Freedman ND, Haiman CA, et al. Association of coffee consumption with total and cause-specific mortality among nonwhite populations. *Ann Intern Med* 2017;167:228-235.

Gunter MJ, Murphy N, Cross AJ, et al. Coffee drinking and mortality in 10 European countries: A multinational cohort study. *Ann Intern Med* 2017;167:236-247.

Travel throughout the world and one will find coffee to be one of the most popular drinks consumed. In the United States alone, about three-quarters of adults drink coffee and nearly half drink it daily.[1] One also will find coffee bean preparations to vary tremendously depending on the coffee culture. From drip coffee to espresso, from light roast to dark, techniques vary widely and affect both the caffeine and antioxidant content of the beans. Frequently, coffee is consumed with added cream, milk, and/or sugar, which increase the caloric content significantly. Considering the quantity of coffee consumed worldwide, it is important for healthcare providers to study closely the potential health benefits of drinking coffee across culture and race.

Summary Points

- Coffee consumption decreases the risk of dying from liver disease, including liver-associated digestive disease, cirrhosis, and liver cancer, in Europeans.
- The risk of ovarian cancer may be higher in women who are regular coffee drinkers.
- As coffee consumption increases, the risk of death decreases in Japanese-Americans, Latinos, African-Americans, and Caucasians.
- Coffee contains multiple health-promoting chemicals such as antioxidants and lignans.

Two large prospective cohort studies, the European Prospective Investigation into Cancer and Nutrition (EPIC) and the Multiethnic Cohort Study of Diet and Cancer (MEC), yielded data useful in analyzing the potential health benefits of coffee consumption. Uncontrolled confounding variables, such as smoking, pre-existing illness, alcohol intake, body mass index, and exercise, make it difficult to generalize the health benefits of coffee consumption. The authors of the EPIC and MEC trials attempted to control for confounding variables using multiple statistical methods.

EUROPEAN PROSPECTIVE INVESTIGATION INTO CANCER AND NUTRITION

The EPIC study included 521,330 people aged 35 years and older from 10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom). The intent was to evaluate whether coffee consumption was associated with all-cause and cause-specific mortality. The authors of this large study generated baseline data and followed up with participants an average of 16.4 years. Only two data points were generated: coffee consumption at baseline and 16.4 years later. Data generated included coffee consumption but also data for a subcohort including biomarkers for liver function, metabolism, and inflammation (ALT, AST, GGT, Alk Phos, C-reactive protein [CRP], high-density lipoprotein, lipoprotein (a), and hemoglobin A1c [HbA1c]). The researchers found that participants in the highest quartile of coffee consumption had a statistically significant lower risk of dying. This inverse association applied to both men and women.

How coffee is prepared before consumption varies widely in these European countries. For example, espresso is small in quantity but concentrated in phytochemicals. One serving of Italian espresso is not the same as one cup of coffee in the United Kingdom. Special statistics were used to account for these differences, using country-specific quartiles and looking at trends across exposure groups. Four quartiles of consumption were generated (low, medium-low, medium-high, and high). The authors analyzed the volume of coffee consumed (zero cups, less than one cup, one to less than two cups, two to less than three cups, more than three cups per day) with one cup = 237 mL coffee. Participants in the highest quartile of coffee consumption had a lower risk of death from all causes. Similar inverse associations and linear trends were found with caffeinated and decaffeinated coffee.

Multivariable models adjusted for body mass index, physical activity, smoking status (type, frequency, duration), education, menopausal status, use of oral contraceptives or hormone replacement therapy, alcohol consumption, total caloric intake per day, consumption of red and processed meats, and consumption of fruits and vegetables. When the data were adjusted for these variables, there continued to be an inverse association between mortality and coffee consumption.

All-cause mortality was recorded. Specific causes of death investigated are listed in Table 1. Both men and women in the highest quartile of coffee consumption had a statistically significant decreased risk of dying from all gastrointestinal diseases (P trend < 0.001; hazard ratio [HR], 0.41 for men; HR, 0.60 for women). The gastrointestinal (GI) disease category included diseases of the oral cavity, esophagus, stomach, pancreas, gall bladder, liver, and intestines. More than one-third of the deaths from GI disease were from liver disease. GI disease was broken down further into liver disease and non-liver GI disease. Daily, frequent coffee drinking was associated with a decreased risk of dying from liver disease (sexes combined HR, 0.20; 95% confidence interval [CI], 0.13-0.29), cirrhosis (HR, 0.21; 95% CI, 0.13-0.34), and liver cancer, whereas coffee consumption did not decrease the risk of death from non-liver digestive diseases (HR, 0.81) conclusively. Interestingly, in the subcohort, liver function biomarkers (ALP, ALT, AST, and GGT) were significantly lower in people who drank coffee regularly compared with those who rarely or never drank coffee. In women only, higher coffee consumption was associated with lower CRP, HbA1c, lipoprotein (a), and higher high-density lipoprotein. This may account for the decreased risk of dying from heart disease in women who drank more coffee (HR, 0.70; 95% CI, 0.55-0.90). Finally, women who frequently drank coffee had an increased risk of dying from ovarian cancer (HR, 1.31; 95% CI, 1.07-1.61) when compared to women who did not drink coffee.

MULTIETHNIC COHORT STUDY OF DIET AND CANCER

Until the MEC study, data in non-white populations evaluating coffee consumption and risk for total and

Table 1: Cause-specific Mortality Risk and Coffee Consumption

Cause-specific mortality	Decreased risk with coffee intake	Increased risk with coffee intake	Risk unknown	Not related	Men	Women
Digestive disease	X				X	X
Liver disease	X				X	X
Non-liver digestive disease			X			
Cirrhosis (alcoholic and non-alcoholic)	X				X	X
Cerebrovascular disease	X					X
Ovarian cancer		X				X
Lung cancer	X				X	
Liver cancer	X				X	X
Respiratory disease				X		
External causes				X		
Suicide	X				X	

cause-specific mortality were sparse. This study included 185,855 African-Americans, Native Hawaiians, Japanese-Americans, Latinos, and whites between 45 to 75 years of age and living in the United States at the time of recruitment. The investigators followed these participants for an average of 16.2 years and assessed coffee intake with a food-frequency questionnaire. Like the EPIC study, the MEC study also had only two data points: the baseline and the single follow-up. Coffee intake was reported in six categories: none, one to three cups per month, one to six cups per week, one cup per day, two to three cups per day, and more than four cups per day. Drinking coffee decreased the risk of dying across ethnic groups analyzed, even after adjustment for confounding variables: one cup per day (HR, 0.88; 95% CI, 0.85-0.91), two to three cups per day (HR, 0.82; 95% CI, 0.79-0.86), and more than four cups per day (HR, 0.82; 95% CI, 0.78-0.87). Decaffeinated and caffeinated coffee appear to have similar benefit.

This study was analyzed to control for confounding variables and tease out the specific effect of coffee consumption on mortality. Those in the group of highest consumption of coffee (more than four cups per day) also tended to smoke cigarettes, creating a significant confounding variable in this analysis. Subgroup analyses were conducted for smoking, age, education level, pre-existing heart disease, and pre-existing cancer. A statistically significant inverse association with coffee consumption and mortality was found across these analyses. The association of coffee consumption and mortality was examined across five ethnic groups. An inverse association between coffee consumption and mortality was found with all groups. (*See Table 2.*) Statistical significance was reached in all populations except Native Hawaiians.

Total mortality and cause-specific mortality were analyzed in this cohort. After adjustment for confounders, there was a significant inverse association between increasing coffee consumption and all-cause mortality. The HR decreased as coffee consumption increased. The HR for death was 1.00 for one to three cups of coffee per month. In those who consumed one to six cups per week, the HR was 0.97. The lowest HR was 0.82 (95% CI, 0.78-0.87) for two groups: those who consume two to three cups per day and four or more cups of coffee per day. Consumption of both decaffeinated (P trend = 0.008) and caffeinated (P trend < 0.001) coffee decreased the risk of death. This association was similar in both women and men.

To determine if coffee consumption decreased the risk of death from specific causes, the authors analyzed the 10 leading causes of death in the United States. They found a statistically significant inverse association with coffee consumption and cardiovascular disease (P trend < 0.001), cancer (P trend = 0.023), chronic lower respiratory disease (P trend 0.015), stroke (P trend < 0.001), diabetes (P trend = 0.009), and kidney disease (P trend < 0.001). There was no significant association between coffee drinking death from influenza, pneumonia, Alzheimer's disease, accidents, and intentional self-harm.

■ COMMENTARY

Is coffee an elixir of life? These two studies seem to answer with a resounding "yes." Although the authors

Table 2: Coffee Consumption and Mortality in Various Ethnic Populations

Ethnicity	*P* value	HR, 1-3 cups/month	HR, 1-6 cups/month	HR, 1 cup/day	HR, > 2 cups/day
African-Americans	0.001	0.95	0.94	0.86	0.80
Japanese-Americans	< 0.001	0.94	0.94	0.85	0.80
Latinos	0.002	1.09	1.13	1.07	0.99
Caucasians	0.003	1.07	0.93	0.88	0.81
Native Hawaiians	0.141	1.07	1.22	0.86	0.94

generated compelling data and did their best to control for multiple confounding variables, there is not enough cross-cultural data to say definitively that coffee consumption benefits everyone all the time. In each study, only two coffee consumption data points, based on surveys, were generated over nearly 16.5 years. We do not know if coffee was consumed steadily for 16 years, just that it was at the beginning and at the end of the studies. To better assess the frequency and quantity of coffee consumption, multiple data points over several years would strengthen the argument that drinking coffee decreases the risk of death.

In addition, coffee is a popular beverage in many other countries that were not included in the study. According to the International Coffee Organization, the people of Finland consume more coffee per capita than other countries, but this was not included in the European study.[2] All the participants in the NEC cohort were from the United States, which ranks 26th in coffee consumption per capita worldwide. Future studies generating data from the countries with higher coffee consumption would provide better data to evaluate the relationship of coffee to mortality more completely.

Previous studies have linked coffee with significant health benefits.[3,4] Coffee consumption has been shown to reduce insulin resistance and inflammation, lowering the risk for developing diabetes, metabolic syndrome, heart disease, and cancer. The EPIC researchers found that coffee improved liver function biomarkers and reduced the risk of dying from liver disease.

The health benefits of coffee can be attributed to the many phytochemicals naturally present in coffee.[5] These include antioxidants, chlorogenic acid, and caffeic acid. Caffeic acid has been shown to reduce inflammation, induce apoptosis, and have an anticancer effect. Kahweol and cafestol activate enzymes that alter carcinogens and render them harmless. Coffee also is a source of lignans, compounds that cell culture and animal studies suggest may optimize estrogen metabolism, decrease cancer cell growth, and promote apoptosis of cancer cells.[6] The phytochemical content of coffee varies depending on where the beans are grown and how they are prepared for consumption. Laboratory studies show instant coffee may be lower in antioxidants than brewed coffee,[7] although more research is needed. Future investigation is needed to learn where the beans richest in these phytochemicals grow and what production methods favor high levels of phytochemicals.

In a recent study on healthy adults, drinking up to five cups of coffee per day was not associated with acute toxicity or adverse cardiovascular, behavioral, bone, calcium, or developmental and reproductive effects.[8] For now, clinicians can be confident that patients who drink moderate amounts of coffee (up to four cups) daily are not harming themselves and, in fact, likely are benefiting their health and decreasing their risk of death. However, people with a tendency to anxiety, insomnia, and diarrhea need to be careful with coffee, as the stimulant and laxative effect of coffee can exacerbate these conditions. ■

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Can Herbs Improve Endurance? Adaptogens and Athletic Performance

By Ted Wissink, MD, Bryan Lamoreau, MD, and Craig Schneider, MD

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Dr. Wissink, Dr. Lamoreau, and Dr. Schneider report no financial relationships relevant to this field of study.

The term "adaptogen" appears to have been coined by Russian researchers in the 1950s to describe medicinal botanicals with the potential to increase stamina and survival in stressful environments.[1] The concept appears to have been inspired by the use of stimulants to enhance mental and physical performance among Russian fighter pilots and submarine crews during World War II.[2] Among the first adaptogen studies published in Soviet Union World War II military journals was *Schisandra chinensis*. Initial interest in *S. chinensis* arose from ethnopharmacological research from the late 19th and early 20th century noting that these berries and seeds were used by Nanai hunters as a tonic to reduce thirst, hunger, and exhaustion and to improve night vision.[1]

After World War II, Russian interest in gaining a competitive advantage for its military extended to its athletes and cosmonauts, fueling further research into other adaptogens. In the 1960s, a scientist named Israel Brekhman began his search to develop drugs from natural substances to stimulate the intrinsic adaptive mechanisms of an organism to help survival in situations of intense and prolonged stress, while maintaining capability for physical and mental work.[3] Brekhman began by investigating Asian ginseng (aka *Panax ginseng*), long regarded as the "longevity herb" in traditional Chinese medicine. However, Asian ginseng did not grow in the Soviet Union and was costly to import. This led him to expand his search to *Eleutherococcus senticosus*, which he termed Siberian ginseng.[3] Eventually Brekhman and his colleague Nicolai Lazarev built a team of researchers who conducted nearly 3,000 clinical trials and experiments on adaptogens. After the collapse of the Soviet Union, clinical studies on adaptogens continued but at a slower pace as funding became more scarce.

This article summarizes the results from a literature search on more recent clinical studies on several adaptogens. The most clinical research in the area surrounded athletic performance, so the review will focus on that outcome.

Summary Points

- Data support the use of several adaptogenic plants for the enhancement of athletic performance.
- Four plants — eleuthero, cordyceps, rhodiola, and ashwagandha — are mentioned most often in the literature and commercial products.
- Of these, the two with the strongest evidence (and their dosing) are: eleuthero (800-1,200 mg daily) and ashwagandha (300-500 mg BID).

ELEUTHERO

Siberian ginseng or eleuthero (*E. senticosus*) is a thin, thorny shrub native to the forests of southeastern Russia, northern China, Japan, and Korea.[4] Eleutherosides are the group of active chemicals derived from the root and rhizome of eleuthero.[5] Siberian ginseng root extract has been used safely in clinical trials lasting up to three months, with the most commonly reported side effects being diarrhea and insomnia.[6] When used orally and appropriately long term, Siberian ginseng has been used in combination with low-dose calcium plus vitamin D3 for up to one year with no significant side effects.[7] Anecdotal reports suggest that taking Siberian ginseng for longer than two months without a two- to three-week break is not recommended.[8]

Early studies concluding eleuthero improves endurance exercise, oxygen uptake, and overall performance in athletes were methodologically flawed. The authors of these studies only used a single-blind protocol with no crossover design.[9,10] In a review article of five studies with good methodology, researchers found no effect of eleuthero raw herb 800 to 1,200 mg/day for one to six weeks on cardiorespiratory fitness, fat metabolism, and endurance performance.[11]

In 2010, Kuo et al published a double-blind, placebo-controlled, crossover study of nine recreationally trained male college students using 800 mg/day of raw dried root and rhizome of eleuthero.[12] The participants already were engaged in a school tennis team, were training 15-16 hours per week, and were not consuming eleuthero or any other nutritional supplement. Baseline assessments determined peak oxygen uptake (VO_2 peak) during a high-intensity endurance workout on a stationary bicycle. VO_2 peak was determined with the following criteria: 1) participant perceived exertion (RPE) using a Borg's 20-point rating scale when > 19; 2) respiratory exchange ratio (RER) > 1.1; and 3) reaching age-predicted maximum heart rate. Then, participants were given either eleuthero or a placebo 800 mg/day for eight weeks, followed by a four-week washout period, after which participants received the other intervention for eight weeks. Participants were asked to maintain their normal training pattern and diet habits during the 20 weeks of the study. For the 24 hours prior to each exhaustion ride, participants were asked to refrain from exercise, caffeine, and alcohol consumption, and to consume the same meal one hour before the task. Testing occurred at the same time of day. During exercise, blood sampling was done at rest, at 15 minutes of exercise, at 30 minutes of exercise, and at exhaustion. Glucose and plasma free fatty acid (FFA) concentrations were measured each time.

After eight weeks of supplementation, VO_2 peak of the eleuthero group was significantly higher than the placebo group. RPE increased slightly for both placebo and eleuthero groups, but the eleuthero RPE was significantly higher than placebo. Resting heart rate showed no difference, but maximal heart rate increased significantly ($P < 0.05$) in the eleuthero group (E = 190 vs. P = 182). Significant differences also were found in the RER at 30 minutes. The blood parameter analysis showed FFA levels were higher at 30 minutes (E = 298 µM vs. P = 265 µM) and at exhaustion (E = 343 µM vs. P = 287 µM) in the eleuthero group and were significantly higher than placebo. Significant differences ($P < 0.05$) were found with the RER at 30 minutes (E = 0.90 vs. P = 0.96). Glucose levels were decreased significantly at 30 minutes (E = 82.4 mg/dL vs. P = 88.6 mg/dL) and exhaustion (E = 86.6 mg/dL vs. P = 92.8 mg/dL).

Based on these results, eleuthero supplementation enhanced endurance time, elevated cardiovascular functions, and altered metabolism of plasma FFA and glucose during the 75% VO_2 peak exercise to exhaustion on a stationary bicycle. The authors theorized that duration of treatment was the important factor to explain the positive results in this study (eight weeks) compared to negative results in prior studies (less than six weeks). Eleuthero supplementation also seemed to increase FFA availability by increasing fat oxidation, sparing muscle glycogen. They concluded eleuthero may be an effective nutritional supplement for endurance athletes, but the exact mechanisms involved need further investigation.

The only side effect reported was mild insomnia in one participant for the first day of eleuthero supplementation. The authors reported no financial interest in eleuthero as a supplement.

CORDYCEPS AND RHODIOLA

Cordyceps sinensis is a naturally occurring parasitic fungus native to the Tibetan Plateau. It is also known as the caterpillar fungus or "DongChongXiaCao" (Summer-plant, Winter-worm), which colonizes the larvae of Hepialidae moths, filling their bodies with mycelium. Traditional Tibetan and Chinese medicine practitioners used it for its ability to invigorate the body and reduce fatigue[13] by its function to "replenish the kidney and soothe the lung."[14]

Although wild Cordyceps increasingly is rare in its natural habitat and thus very expensive, a refined standardized fermentation product, Cs-4, is produced from mycelial strains isolated from wild Cordyceps and contains similar chemical constituents (0.14% adenosine, 5% mannitol; Cs-4, CordyMax).

Researchers from UCLA conducted a double-blind, placebo-controlled, prospective study of the commercially available Cs-4 product on 20 men and women between 50 and 75 years of age. Subjects were randomized to Cs-4 or placebo (starch) capsules, taken three times a day with water or food for 12 weeks. Exercise performance was evaluated on a cycle ergometer, while physical fitness was assessed through measurements of VO_{2max} and gas exchange metabolic threshold. Dropouts in each group were similar at study completion, with eight in the Cs-4 group and seven in the placebo group. From baseline, the Cs-4 group had an increase in metabolic threshold of 10.5% ($P = 0.022$), while the placebo group decreased by 3.9% ($P = 0.182$), with similar results occurring in ventilatory threshold. There were no other significant differences in VO_{2max}, heart rate, maximum work rate or maximum ventilation, blood pressure, lactic acid peak level, recovery, or heart rate recovery. The authors believed this small but consistent improvement in aerobic performance of subjects receiving Cs-4 would translate to meaningful improvements in activities of daily living in older adults if it could be reproduced in larger studies.[15]

Like cordyceps, *Rhodiola crenulata*, which is closely related to *Rhodiola rosea* and grows mostly in the Tibetan region, is another botanical native to cold, mountainous regions of Asia, Europe, and high altitudes in the Arctic. It also has a long history of use in traditional Asian medical systems for a wide variety of conditions, including improved physical endurance and

work performance, resistance to high-altitude sickness, mental capacity, and longevity. Today, rhodiola most commonly is used for increasing energy, endurance, strength, and mental capacity.[16]

Chen et al conducted a double-blind, placebo-controlled trial on 18 male long-distance track and field athletes during high-altitude training (2,200 meters).[17] One group received a placebo (starch) and the other group received *R. crenulata* plus *C. sinensis* (RC, 1,000 mg capsule) twice daily with breakfast and dinner. The groups participated in intensive exercise training, which included distance, speed, endurance, and strength workouts. Measurements conducted at sea level post-intervention showed that the RC group run time to exhaustion was prolonged significantly compared to placebo (placebo: +2.2% vs. RC: +5.7%; $P < 0.05$). Additionally, the decline in parasympathetic activity in the RC group was attenuated (placebo: -51% vs. RC: -41%; $P < 0.05$), and endogenous EPO production was lower compared to the placebo group (placebo: ~48% higher than RC values; $P < 0.05$.) There were no differences in VO_{2max}, red blood cell, hemoglobin, testosterone, or cortisol levels. The authors concluded that RC improves aerobic exercise capacity and produces anti-stress reactions that may increase adaptations to exercise training at high altitude.[17] The authors of these human trials disclosed no competing financial interests.

ASHWAGANDHA

Ashwagandha (*Withania somnifera*), also known as Indian ginseng or winter cherry, is a dense shrub with roots that have been used extensively in Ayurvedic medicine for 3,000 years as a general tonic to help the body adapt to stress. The root contains a number of antioxidants as well as flavonoids, alkaloids, and steroidal lactones, which are thought to confer the beneficial effects in the body.[18] Recent advances have been made to elucidate the biological properties of *W. somnifera* and its potential role in health benefits.

A randomized, double-blind, prospective clinical study of 57 male subjects 18 to 50 years of age with minimal experience in resistance training were divided into treatment and placebo groups. Participants agreed to refrain from tobacco, alcohol, and anti-inflammatory agents during the study and had to be cleared for participation by their physician. The treatment group reviewed 300 mg Ashwagandha root twice daily, while the control received a starch placebo. Muscle strength, muscle size, body composition, serum testosterone level, and muscle recovery was measured at baseline and then again after eight weeks of a resistance training program. The three-days-weekly training program targeted large muscle groups with instruction on proper technique. Muscle strength was measured using the one repetition maximum for bench press and leg extension exercise. Serum creatine kinase was used as a marker of muscle injury to evaluate recovery. The treatment group had significantly greater improvement in muscle strength in both exercises (26.4 kg vs. 46.0 kg on the bench press [$P = 0.001$]; 14.5 kg vs. 19.8 kg, [$P = 0.04$]), increase in size of the chest (1.4 cm vs. 3.3 cm; $P = 0.001$) and arms (5.3 cm vs. 8.6 cm; $P = 0.01$), lower creatine kinase (1,307.5 U/L decrease vs. Ashwagandha 1,462.6 U/L; $P = 0.03$), a greater increase in testosterone levels (18.0 ng/dL vs. Ashwagandha: 96.2 ng/dL; $P = 0.004$), and a greater decrease in body fat percentage (1.5% vs. 3.5%; $P = 0.03$). The authors concluded that Ashwagandha may be useful to take in a resistance training program.[19]

Shenoy et al studied supplementation of Ashwagandha in 40 elite cyclists (20 of each gender), defined as participation of the athlete in at least state-level events.[20] Participant ages ranged from 18-27 years and they took no other supplements or performance aides. They were divided into treatment (500 mg capsules of standardized Ashwagandha root extract twice daily) and placebo (starch tablets). A baseline graded-exercise test (GXT) was performed on a treadmill with electronic heart rate monitor and full nose-mouth piece to measure VO_{2max}, respiratory exchange ratio (RER), and total time for the athlete to reach their volitional point of exhaustion. After eight weeks of supplementation, the same testing was performed. The Ashwagandha group but not the placebo group experienced significant improvement in several parameters. Specifically, VO_{2max} increased 13% ($P = 0.001$), and time to exhaustion improved by over full minute ($P = 0.0010$). A subanalysis showed that males were more responsive to the treatment than females. The authors concluded that Ashwagandha significantly improved aerobic performance in well-trained athletes, a group in which it usually is quite difficult to detect minor changes.[20]

Sandhu et al measured a number of variables, including $VO_{2\,max}$, velocity, power, and blood pressure, in a single-blind, randomized study of 40 healthy young college students, 22 female and 18 males, mean age 20.6 years, and mean body mass index (BMI) 21.9 kg/m^2.[21] Ten participants received Ashwagandha alone (500 mg standardized aqueous root extract), while another 10 received *Terminalia arjuna* alone (500 mg aqueous bark extract of this botanical commonly used in Ayurvedic medicine for heart conditions). Ten received both Ashwagandha and *T. arjuna*, and 10 received a placebo capsule (flour). Although generally healthy, none of the participants had participated in regular exercise for the prior six months. Velocity was measured using a multiple camera program called Kinematic Measuring System (KMS) during a sprint. Power of the lower limbs during vertical jumps also was measured using KMS. Balance was measured with a wobble board program called Kinematic. Peak oxygen consumption was measured with a computer

controlled Vista Turbo Trainer machine. The researchers measured systolic and diastolic blood pressure and monitored subjects' BMI. All variables were collected at baseline and at eight weeks. Compliance with medications was ensured by daily administration after a meal.

Ashwagandha significantly increased velocity ($P = 0.005$), power ($P = 0.002$), and VO_{2max} ($P = 0.005$). There was no improvement in balance or blood pressure. *T. arjuna* significantly increased VO_{2max} and lowered resting systolic blood pressure. The combination also resulted in significantly increased VO_{2max}, velocity, and power, as well as improved systolic blood pressure, but not significantly beyond either herb alone. There were no changes in any variables for the placebo group. No side effects were reported, but authors noted that future studies are needed that are longer in duration.[21]

Choudhary et al conducted a randomized, double-blind, placebo-controlled study on 50 young healthy male and female adults aged 20-45 years with a BMI range of 18.5-24.9 kg/m^2.[22] Participants were randomized to placebo (sucrose) or Ashwagandha (KSM-66 by Ixoreal Biomed, containing 300 mg of standardized root extract) capsules twice daily for 12 weeks. Cardiorespiratory endurance was evaluated with a 20-meter shuttle run test, which is used commonly as a more feasible, but still reliable, means of calculating VO_{2max}. The researchers also administered the World Health Organization Quality of Life (WHO-QOL) self-reported questionnaire, which includes a subdomain for physical health. These were evaluated at baseline, four, eight, and 12 weeks. Treatment with the Ashwagandha (n = 24, one subject dropped out) compared to placebo (n = 25) resulted in a significant improvement in VO_{2max} from baseline ($P < 0.0001$) at week 8 (4.91 and 1.42, respectively) and at week 12 (5.67 and 1.86, respectively). The WHO-QOL scores also improved for all domains including physical health in the Ashwagandha group by week 12 ($P < 0.05$). The authors concluded that Ashwagandha enhanced cardiorespiratory endurance and improved quality of life in healthy adults, but more studies are needed to see if this generalizes to all populations.[22]

DISCUSSION AND RECOMMENDATIONS

These four adaptogens are the most cited in the literature for athletic endpoints, and seem to be the main components in many herbal combination dietary supplements marketed to athletes for performance improvement. Caution should be used in interpreting these studies, since the literature search found no recent negative studies on these adaptogens and publication bias may be present. Also, the populations studied generally consisted of healthy adults, including high-level athletes; thus, the generalizability of these findings remains unclear.

For the average patient seeking advice on athletic performance-enhancing combination products, there is little in the literature to suggest additive or synergistic effects of these adaptogens, and patients should be advised caution. In reviewing the labels on several of these products, it is evident that dosing of the herbs in combination products often is lower than that used in the studies. Several products also included stimulants like caffeine, presumably as an attempt to give the user a perceived increase in energy directly after taking the product.

Instead, for interested athletes, we suggest recommending a single adaptogen in appropriate dosing based on the studies reviewed. Eleuthero (800-1,200 mg dried raw herb daily) and Ashwagandha (300-500 mg standardized root extract BID) have the strongest evidence base in the literature. Given that the studies did not extend beyond two to three months, it would be best to encourage a holiday of several weeks after that time. It also would be advisable to review common side effects and run an interaction check with all of a patient's prescription medications. Because of their proposed immunologic mechanism of action, adaptogens may best be paused during bacterial infections as well; otherwise, there are no clear contraindications. As is often the case in medicine, statistical significance does not always mean clinical relevance, and expectations should be realistic. As important as the modest benefits observed in measures of endurance and recovery, the improvements in ratings of perceived exertion and quality of life may be even more relevant. ■

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1. A secondary analysis of data about the relationship between gluten intake and coronary heart disease (CHD) showed an inverse association between which of the following?
a. Overall gluten intake and CHD
b. Refined grain intake and CHD
c. Whole grain intake and CHD
d. Multigrain intake and CHD

2. What statement is true regarding coffee consumption?
a. Coffee consumption increases all-cause mortality.
b. Coffee consumption negatively increases risk of death from digestive disease.
c. Drinking coffee on a daily basis decreases liver function biomarkers.
d. All of the above

3. As reviewed in the article about adaptogens and athletic performance, all of the following plants have shown benefits in clinical trials *except*:
a. *Cordyceps sinensis*.
b. *Rhodiola rosea/crenulata*.
c. *Echinacea purpurea*.
d. *Eleutherococcus senticosus*.

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