



# ENERGY+

POMEGRANATE LIME

All-Natural Mental Energy &  
Motivation



## TECHNICAL DATA

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# ENERGY+

A next-generation mental energy product that delivers rapid improvements in brain and physical performance, without the jitters or crash you might get from many high-stimulant or high-sugar energy drinks.\*

## KEY INGREDIENTS

**Matcha Green Tea** - packed with catechins that deliver both potent antioxidant protection and metabolism-enhancing effects. Matcha's high content of L-theanine also helps to energize the body while calming and focusing the mind.\*

**Guayusa Leaf** (*pronounced gwhy-you-sa*) - an Amazonian leaf naturally packed with caffeine, polyphenols, and 15 essential amino acids. Guayusa leaf provides clean, focused energy. Traditionally referred to as the "night watchman" by native hunters, guayusa tea helps to improve physical energy and focused mental alertness.\*

**Pomegranate Seed extract** - contains specialized polyphenols that help balance normal inflammatory pathways and open up blood vessels to stimulate blood circulation and boost vitality.\*

**Asian Apple Polyphenols** (Applephenon®) - carefully extracted from specially selected wild green unripe apples sourced from Central Asia (where apples originated and were first cultivated thousands of years ago). Applephenon delivers powerful antioxidant properties from its optimized profile of proanthocyanidins, that deliver both "1st brain" and "2nd brain" effects to support mental and physical energy benefits.\*

**New Zealand Pine Bark Polyphenols** (*Enzogenol™*) - produced from the ultra-clean New Zealand pine bark using proprietary pure water-only environmentally friendly extraction method. The finished extract is rich in OPCs (oligomeric proantho-cyanidins) that are known for their wide range of benefits in cellular protection, cardiovascular performance, alleviation of fatigue, memory enhancement, and enhanced mental acuity.\*

**French Grape Seed Polyphenols** (*Enovita®*) - contains polyphenol flavonoids with both antioxidant and anti-inflammatory properties. In particular, specific research on grape seed extracts have shown biological properties, including cardioprotective, neuroprotective, and hepatoprotective activities, as well as specific "2nd brain" energy benefits via direct inflammatory-balancing effects within the GI tract. Enovita is a proprietary proanthocyanidin-rich extract made exclusively with grape seeds from white wine production and using only water as extraction solvent.\*

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## CLINICAL STUDIES

### **Food Res Int. 2017 Sep;99(Pt 1):72-83.**

*An intervention study on the effect of matcha tea, in drink and snack bar formats, on mood and cognitive performance.*

**Dietz C, Dekker M, Piqueras-Fizman B.**

#### **Abstract**

Matcha tea is gaining popularity throughout the world in recent years and is frequently referred to as a mood-and-brain food. Previous research has demonstrated that three constituents present in matcha tea, l-theanine, epigallocatechin gallate (EGCG), and caffeine, affect mood and cognitive performance. However, to date there are no studies assessing the effect of matcha tea itself. The present study investigates these effects by means of a human intervention study administering matcha tea and a matcha containing product. Using a randomized, placebo-controlled, single-blind study, 23 consumers participated in four test sessions. In each session, participants consumed one of the four test products: matcha tea, matcha tea bar (each containing 4g matcha tea powder), placebo tea, or placebo bar. The assessment was performed at baseline and 60min post-treatment. The participants performed a set of cognitive tests assessing attention, information processing, working memory, and episodic memory. The mood state was measured by means of a Profile of Mood States (POMS). After consuming the matcha products compared to placebo versions, there were mainly significant improvements in tasks measuring basic attention abilities and psychomotor speed in response to stimuli over a defined period of time. In contrast to expectations, the effect was barely present in the other cognitive tasks. The POMS results revealed no significant changes in mood. The influence of the food matrix was demonstrated by the fact that on most cognitive performance measures the drink format outperformed the bar format, particularly in tasks measuring speed of spatial working memory and delayed picture recognition. This study suggests that matcha tea consumed in a realistic dose can induce slight effects on speed of attention and episodic secondary memory to a low degree. Further studies are required to elucidate the influences of the food matrix.

### **Curr Pharm Des. 2017 Jan 5.**

*Effect of Green Tea Phytochemicals on Mood and Cognition.*

**Dietz C, Dekker M.**

#### **Abstract**

BACKGROUND:

Green tea is traditionally known to induce mental clarity, cognitive function, physical activation and relaxation. Recently, a special green tea, matcha tea, is rapidly gaining popularity throughout the world and is frequently referred to as a mood- and brain food. Matcha tea consumption leads to much higher intake of green tea phytochemicals compared to regular green tea. Previous research on tea constituents caffeine, L-theanine, and epigallocatechin gallate (EGCG) repeatedly demonstrated benefits on mood and cognitive performance. These effects were observed when these phytochemicals were consumed



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separately and in combination.

### METHODS:

A review was conducted on 49 human intervention studies to summarize the research on acute psychoactive effects of caffeine, L-theanine, and EGCG on different dimensions of mood and cognitive performance.

### CONCLUSIONS:

Caffeine was found to mainly improve performance on demanding long-duration cognitive tasks and self-reported alertness, arousal, and vigor. Significant effects already occurred at low doses of 40 mg. L-theanine alone improved self-reported relaxation, tension, and calmness starting at 200 mg. L-theanine and caffeine combined were found to particularly improve performance in attention-switching tasks and alertness, but to a lesser extent than caffeine alone. No conclusive evidence relating to effects induced by EGCG could be given since the amount of intervention studies was limited. These studies provided reliable evidence showing that L-theanine and caffeine have clear beneficial effects on sustained attention, memory, and suppression of distraction. Moreover, L-theanine was found to lead to relaxation by reducing caffeine induced arousal.

## J Sci Food Agric. 2017 Sep;97(12):3929-3936.

*Guayusa (Ilex guayusa L.) new tea: phenolic and carotenoid composition and antioxidant capacity.*

García-Ruiz A, Baenas N, Benítez-González AM, Stinco CM, Meléndez-Martínez AJ, Moreno DA, Ruales J.

### Abstract

#### BACKGROUND:

Guayusa (*Ilex guayusa Loes*) is an evergreen tree native of South America that grows particularly in the upper Amazon region of Ecuador. For its health benefits, it has been cultivated and consumed since ancient times by Amazon indigenous tribes.

#### RESULTS:

A total of 14 phenolic compounds were identified and quantified. Chlorogenic acid and quercetin-3-O-hexose were the main representatives of the hydroxycinnamic acids and flavonols, respectively. Five carotenoids were identified, showing lutein the highest concentration. Guayusa leaves revealed high antioxidant capacity determined by two analytical methods, DPPH and ORAC. The industrial processing applied to the leaves modified the composition of bioactive compounds and antioxidant capacity of guayusa. In general, blanched guayusa retained the concentration of phenolic compounds and some carotenoids and similar antioxidant capacity as untreated green leaves. In contrast, fermentation reduced the content of bioactive compounds and showed the lowest antioxidant capacity.

#### CONCLUSION:

Therefore, blanched guayusa has potential for product development as a functional ingredient in the food industry.

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### **Ciba Found Symp. 1994;185:106-12.**

*Amazonian ethnobotany and the search for new drugs.*

Schultes RE.

#### **Abstract**

Tropical rain forests offer enormous prospects for the discovery of new drugs for use in Western medicine. The Amazon supports 80,000 species of higher plants and a diverse Indian population. Focusing attention on those plants used as medicines by indigenous peoples is the most efficient way of identifying the plants that contain bioactive compounds. There is an urgent need for more ethnobotanists and ethnopharmacologists to be trained to document as much information as possible before it and the plants are lost through destruction of the rain forest and acculturation of the indigenous peoples. Ethnobotanical studies have identified plants documented by early travellers; these include Paullinia yoco and Ilex guayusa which are used as stimulants and have been shown to be rich in caffeine. Studies of the hallucinogen prepared from Banisteriopsis caapi have shown that the native people know which plants to add to the mixture to lengthen and intensify the intoxication produced by the beta-carboline alkaloids in the plant. Three major snuffs are used in the Amazonia; the plants from which they are derived have been identified. One of the snuffs also has antifungal and curare-like activities; chemical analysis on the active principles has not been done. Several plants are considered as prime candidates for scientific study as sources of useful chemicals for medicine or industry. These include some used to prepare teas or other infusions for treatment of various symptoms of senile dementia.

### **J Ethnopharmacol. 1991 May-Jun;33(1-2):25-30.**

*Ritualistic use of the holly Ilex guayusa by Amazonian Jívaro Indians.*

Lewis WH, Kennelly EJ, Bass GN, Wedner HJ, Elvin-Lewis MP, Fast D.

#### **Abstract**

In Amazonian Peru and Ecuador leaf decoctions of the rainforest holly Ilex guayusa with high caffeine concentrations are used as a morning stimulant. After daily ingestion, ritualistic vomiting by male Achuar Indians, better known as Jívaros, reduces excessive caffeine intake, so that blood levels of caffeine and biotransformed dimethylxanthines do not cause undesirable CNS and other effects. Emesis is learned and apparently not due to emetic compounds.

### **Diabetes Res. 1989 Feb;10(2):69-73.**

*Glycaemic effects of traditional European plant treatments for diabetes. Studies in normal and streptozotocin diabetic mice.*

Swanston-Flatt SK, Day C, Flatt PR, Gould BJ, Bailey CJ.

#### **Abstract**

Twelve plants used for the traditional treatment of diabetes mellitus in northern Europe were studied using normal and streptozotocin diabetic mice to evaluate effects on glucose homeostasis. The plants were administered in the diet (6.25% by weight) and/or as decoctions or infusions in place of drinking water, to

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coincide with the traditional method of preparation. Treatment for 28 days with preparations of burdock (*Arctium lappa*), cashew (*Anacardium occidentale*), dandelion (*Taraxacum officinale*), elder (*Sambucus nigra*), fenugreek (*Trigonella foenum-graecum*), guayusa (*Ilex guayusa*), hop (*Humulus lupulus*), nettle (*Urtica dioica*), cultivated mushroom (*Agaricus bisporus*), periwinkle (*Catharanthus roseus*), sage (*Salvia officinale*), and wild carrot (*Daucus carota*) did not affect the parameters of glucose homeostasis examined in normal mice (basal plasma glucose and insulin, glucose tolerance, insulin-induced hypoglycaemia and glycated haemoglobin). After administration of streptozotocin (200 mg/kg) burdock and nettle aggravated the diabetic condition, while cashew, dandelion, elder, fenugreek, hop, periwinkle, sage and wild carrot did not significantly affect the parameters of glucose homeostasis studied (basal glucose and insulin, insulin-induced hypoglycaemia, glycated haemoglobin and pancreatic insulin concentration). Guayusa and mushroom retarded the development of hyperglycaemia in streptozotocin diabetes and reduced the hyperphagia, polydipsia, body weight loss, and glycated haemoglobin. Mushroom also countered the initial reduction in plasma insulin and the reduction in pancreatic insulin concentration, and improved the hypoglycaemic effect of exogenous insulin. These studies suggest the presence of potentially useful antidiabetic agents in guayusa and mushroom.

### **Int J Toxicol. 2016 Mar-Apr;35(2):222-42.**

***General and Genetic Toxicology of Guayusa Concentrate (Ilex guayusa).***

**Kapp RW Jr, Mendes O, Roy S, McQuate RS, Kraska R.**

#### **Abstract**

Tea from the leaves of guayusa (*Ilex guayusa*) has a long history of consumption by Ecuadorian natives in regions where the plant is indigenous. The tea contains the methylxanthines caffeine and theobromine as well as chlorogenic acids, flavonoids, and sugars. Various studies were performed to evaluate the general and genetic toxicology of a standardized liquid concentrate of guayusa (GC). Guayusa concentrate was found to be negative in in vitro genotoxicity tests including the Ames test and a chromosome aberration study in human lymphocytes. The oral median lethal dose (LD50) of GC was >5,000 mg/kg for female rats. Guayusa concentrate was administered to male and female rats in a 90-day subchronic study at 1,200, 2,500, and 5,000 mg/kg/d of GC and a caffeine-positive control at 150 mg/kg/d corresponding to the amount of caffeine in the high-dose GC group. Effects observed in the GC-treated groups were comparable to those in the caffeine control group and included reductions in body weights, food efficiency, triglycerides values, and fat pad weights and increases in blood chemistry values for serum aspartate aminotransferase, serum alanine aminotransferase, and cholesterol and adaptive salivary gland hypertrophy. No signs of incremental toxicity due to any other components of guayusa were observed. The studies indicate no harmful effects of GC in these test systems.

### **PLoS One. 2016 Oct 20;11(10):e0160305.**

***Pomegranate Supplementation Accelerates Recovery of Muscle Damage and Soreness and Inflammatory Markers after a Weightlifting Training Session.***

**Ammar A, Turki M, Chtourou H, Hammouda O, Trabelsi K, Kallel C, Abdelkarim O, Hoekelmann A, Bouaziz**

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**M, Ayadi F, Driss T, Souissi N.**

### Abstract

#### PURPOSE:

The aim of this study was to investigate the effect of natural Pomegranate juice supplementation on performance and acute and delayed responses of muscle soreness and biomarkers of muscle damage after a weightlifting training session.

#### METHODS:

Nine elite weightlifters (21±0.5 years) performed two Olympic-Weightlifting-sessions after either placebo (PLA) or natural pomegranate juice (POMj) supplementations. Heart rate, blood pressure and blood samples (hematological parameters, muscle damage and C-reactive protein (CRP)) were collected at rest, 3min and 48h after each session. Weightlifting performance, RPE, and DOMS were also assessed after each training session.

#### RESULTS:

T-test showed higher performance (+8.30%) and lower RPE values (-4.37%) using POMj supplementation ( $p < 0.05$ ) in comparison with PLA. For the DOMS values, a significant improvement (13.4%) was shown only for the knee extensors ( $p < 0.01$ ) using the POMj. Compared to PLA condition, POMj attenuated the acute (i.e., 3min) increase of systolic blood pressure (SBP), HR, CK and LDH ( $p < 0.05$ ; -4.46%, -1.81%, -8.75%, -1.64%, respectively) and blunted the significant increase of ASAT, PAL and CRP ( $p > 0.05$ ). Additionally, during the 48h following the training session, POMj improved the recovery kinetic of SBP ( $p < 0.01$ , 7.97%), CK ( $p < 0.001$ , 11.34%), LDH ( $p < 0.05$ , 7.30%) and ASAT ( $p < 0.05$ , 6.77%). Indeed, the present study showed that 48h of recovery associated to natural POMj supplementation was sufficient to reach the resting values of the selected muscle damage markers after intensive training session.

#### CONCLUSION:

Natural POMj seems to ameliorate the capacity to adhere to an intensive training program. Therefore, elite weightlifters are advised to use natural POMj during intensive training program and competition to accelerate muscle recovery.

**Eur J Sport Sci. 2017 Apr;17(3):317-325.**

***Effects of pomegranate extract on blood flow and vessel diameter after high-intensity exercise in young, healthy adults.***

**Roelofs EJ, Smith-Ryan AE, Trexler ET, Hirsch KR1, Mock MG.**

### Abstract

The effects of pomegranate extract (PE) supplementation were evaluated on high-intensity exercise performance, blood flow, vessel diameter, oxygen saturation (SPO<sub>2</sub>), heart rate (HR), and blood pressure (BP). In a randomized, crossover design, nineteen recreationally resistance-trained participants were randomly assigned to PE (1000 mg) or placebo (PL), which were consumed 30 min prior to a repeated sprint ability (RSA) test and repetitions to fatigue (RTF) on bench and leg press. The RSA consisted of ten six-second sprints on a friction-loaded cycle ergometer with 30 s recovery. Brachial artery blood flow and vessel diameter were assessed by ultrasound. Blood flow, vessel diameter, SPO<sub>2</sub>, HR, and BP were assessed at baseline, 30 min post ingestion, immediately post exercise (IPost), and 30 min post exercise

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(30minPost). With PE, blood flow significantly increased IPost RSA (mean difference = 18.49 mL min<sup>-1</sup>; P < .05), and IPost and 30minPost RTF (P < .05) according to confidence intervals (CI). Vessel diameter increased significantly 30minPost RSA according to CI and resulted in a significant interaction IPost and 30minPost RTF (P < .05). With PE, according to CI, average and peak power output increased significantly in sprint 5 of the RSA (P < .05). There was no significant difference between PE and PL for bench (P = .25) or leg press (P = .15) repetitions. Acute PE supplementation enhanced vessel diameter and blood flow, suggesting possible exercise performance enhancement from increased delivery of substrates and oxygen. The acute timing and capsule form of PE may be advantageous to athletic populations due to ergogenic effects, taste, and convenience.

### **Plant Foods Hum Nutr. 2012 Sep;67(3):309-14.**

***Effects of pomegranate juice supplementation on pulse wave velocity and blood pressure in healthy young and middle-aged men and women.***

**Lynn A, Hamadeh H, Leung WC, Russell JM, Barker ME.**

#### **Abstract**

Pomegranate juice may improve cardiovascular risk because of its content of antioxidant polyphenols. We conducted a randomized placebo-controlled parallel study to examine the effect of pomegranate juice on pulse wave velocity (PWV), blood pressure (BP) and plasma antioxidant status (ferric reducing power; FRAP) in 51 healthy adults (30-50 years). Participants consumed 330 ml/day of pomegranate juice or control drink for four weeks. Measurements were made at baseline and at four weeks. There was no effect of the intervention on PWV (P = 0.694) and plasma FRAP (P = 0.700). However, there was a significant fall in systolic blood pressure (-3.14 mmHg, P < 0.001), diastolic blood pressure (-2.33 mmHg P < 0.001) and mean arterial pressure (-2.60 mmHg, P < 0.001). Change in weight was similar in the two groups over the intervention period (P = 0.379). The fall in BP was not paralleled by changes in concentration of serum angiotensin converting enzyme. We conclude that pomegranate juice supplementation has benefits for BP in the short term, but has no effect on PWV. The mechanism for the effect is uncertain.

### **Complement Ther Clin Pract. 2011 May;17(2):113-5.**

***The effects of pomegranate juice consumption on blood pressure and cardiovascular health.***

**Stowe CB.**

#### **Abstract**

Hypertension (HTN) is the most common disease found in patients in primary care [JNC-7 Guidelines. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. Hyper 2003;42:1206.]. It eventually requires medication if lifestyle modifications are not initiated or do not control the blood pressure well enough. The majority of patients would prefer not to have to be medicated to manage their disease, and HTN can be found to be a comorbidity along with diabetes, CAD, and many other cardiovascular diseases. Adverse effects, forgetfulness and patient ignorance are multiple reasons for the hesitancy to begin drug management. Pomegranate juice is rich in tannins, possesses anti-atherosclerotic properties, has anti-aging effects, and potent anti-oxidative



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characteristics. As some antioxidants have been shown to reduce blood pressure, the purpose of this review was to discover the effect of pomegranate juice consumption on blood pressure and cardiovascular health. Pomegranate juice consumption may reduce systolic blood pressure, inhibits serum ACE activity, and is convincingly a heart-healthy fruit [Aviram M, Dornfeld L. Pomegranate juice consumption inhibits serum angiotensin converting enzyme activity and reduces systolic blood pressure. *Athero* 2001;158:195-8.]. More clinical research is needed as a number of the studies discussed include small sample sizes and few studies seem to have been undertaken in the recent 5-10 years.

### **Am J Cardiol. 2009 Oct 1;104(7):936-42.**

***Effects of consumption of pomegranate juice on carotid intima-media thickness in men and women at moderate risk for coronary heart disease.***

**Davidson MH, Maki KC, Dicklin MR, Feinstein SB, Witchger M, Bell M, McGuire DK, Provost JC, Liker H, Aviram M.**

#### **Abstract**

This randomized, double-blind, parallel trial assessed the influence of pomegranate juice consumption on anterior and posterior carotid intima-media thickness (CIMT) progression rates in subjects at moderate risk for coronary heart disease. Subjects were men (45 to 74 years old) and women (55 to 74 years old) with  $\geq$  1 major coronary heart disease risk factor and baseline posterior wall CIMT 0.7 to 2.0 mm, without significant stenosis. Participants consumed 240 ml/day of pomegranate juice (n = 146) or a control beverage (n = 143) for up to 18 months. No significant difference in overall CIMT progression rate was observed between pomegranate juice and control treatments. In exploratory analyses, in subjects in the most adverse tertiles for baseline serum lipid peroxides, triglycerides (TGs), high-density lipoprotein (HDL) cholesterol, TGs/HDL cholesterol, total cholesterol/HDL cholesterol, and apolipoprotein-B100, those in the pomegranate juice group had significantly less anterior wall and/or composite CIMT progression versus control subjects. In conclusion, these results suggest that in subjects at moderate coronary heart disease risk, pomegranate juice consumption had no significant effect on overall CIMT progression rate but may have slowed CIMT progression in subjects with increased oxidative stress and disturbances in the TG-rich lipoprotein/HDL axis.

### **Nutr Rev. 2009 Jan;67(1):49-56.**

***Pomegranate juice: a heart-healthy fruit juice.***

**Basu A, Penugonda K.**

#### **Abstract**

Pomegranate juice is a polyphenol-rich fruit juice with high antioxidant capacity. In limited studies in human and murine models, pomegranate juice has been shown to exert significant antiatherogenic, antioxidant, antihypertensive, and anti-inflammatory effects. Pomegranate juice significantly reduced atherosclerotic lesion areas in immune-deficient mice and intima media thickness in cardiac patients on medications. It also decreased lipid peroxidation in patients with type 2 diabetes, and systolic blood pressure and serum angiotensin converting enzyme activity in hypertensive patients. Thus, the potential

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cardioprotective benefits of pomegranate juice deserve further clinical investigation, and evidence to date suggests it may be prudent to include this fruit juice in a heart-healthy diet.

### **Mol Nutr Food Res. 2009 Mar;53(3):322-31.**

#### ***Vascular action of polyphenols.***

**Ghosh D, Scheepens A.**

#### **Abstract**

Dietary patterns are widely recognised as contributors to cardiovascular and cerebrovascular disease. Endothelial function, the elastic properties of large arteries and the magnitude and timing of wave reflections are important determinants of cardiovascular performance. Several epidemiological studies suggest that the regular consumption of foods and beverages rich in flavonoids is associated with a reduction in the risk of several pathological conditions ranging from hypertension to coronary heart disease, stroke and dementia. The impairment of endothelial function is directly related to ageing and an association between decreased cerebral perfusion and dementia has been shown to exist. Cerebral blood flow (CBF) must be maintained to ensure a constant delivery of oxygen and glucose as well as the removal of waste products. Increasing blood flow is one potential way for improving brain function and the prospect for increasing CBF with dietary polyphenols is extremely promising. The major polyphenols shown to have some of these effects in humans are primarily from cocoa, wine, grape seed, berries, tea, tomatoes (polyphenolics and nonpolyphenolics), soy and pomegranate. There has been a significant paradigm shift in polyphenol research during the last decade. This review summarises our current knowledge in this area and points the way for the development of new types of functional foods targeted to brain health through improving vascular health.

### **Am J Cardiol. 2005 Sep 15;96(6):810-4.**

#### ***Effects of pomegranate juice consumption on myocardial perfusion in patients with coronary heart disease.***

**Sumner MD, Elliott-Eller M, Weidner G, Daubenmier JJ, Chew MH, Marlin R, Raisin CJ, Ornish D.**

#### **Abstract**

Pomegranate juice contains antioxidants such as soluble polyphenols, tannins, and anthocyanins and may have antiatherosclerotic properties. However, no study has investigated the effects of pomegranate juice on patients who have ischemic coronary heart disease (CHD). We investigated whether daily consumption of pomegranate juice for 3 months would affect myocardial perfusion in 45 patients who had CHD and myocardial ischemia in a randomized, placebo-controlled, double-blind study. Patients were randomly assigned into 1 of 2 groups: a pomegranate juice group (240 ml/day) or a placebo group that drank a beverage of similar caloric content, amount, flavor, and color. Participants underwent electrocardiographic-gated myocardial perfusion single-photon emission computed tomographic technetium-99m tetrofosmin scintigraphy at rest and during stress at baseline and 3 months. Visual scoring of images using standardized segmentation and nomenclature (17 segments, scale 0 to 4) was performed by a blinded independent nuclear cardiologist. To assess the amount of inducible ischemia, the summed difference score (SDS) was calculated by subtracting the summed score at rest from the summed stress score. The experimental and control groups showed similar levels of stress-induced

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ischemia (SDS) at baseline ( $p > 0.05$ ). After 3 months, the extent of stress-induced ischemia decreased in the pomegranate group (SDS  $-0.8 \pm 2.7$ ) but increased in the control group (SDS  $1.2 \pm 3.1$ ,  $p < 0.05$ ). This benefit was observed without changes in cardiac medications, blood sugar, hemoglobin A1c, weight, or blood pressure in either group. In conclusion, daily consumption of pomegranate juice may improve stress-induced myocardial ischemia in patients who have CHD.

### **J Alzheimers Dis. 2006 Aug;9(3):287-91.**

***Apple juice concentrate maintains acetylcholine levels following dietary compromise.***

**Chan A, Graves V, Shea TB.**

#### **Abstract**

Oxidative stress contributes to age-related cognitive decline. In some instances, consumption of fruits and vegetables rich in antioxidant can provide superior protection than supplementation with purified antioxidants. Our prior studies have shown that supplementation with apple juice concentrate (AJC) alleviates oxidative damage and cognitive decline in adult (9-12 months) mice lacking ApoE (as a model of increased oxidative stress) and in normal aged (2-2.5 years) mice when challenged with a vitamin-deficient, oxidative stress-promoting diet. Here, we demonstrate that AJC, administered in drinking water, maintains acetylcholine levels that otherwise decline when adult and aged mice are maintained on the above deficient diet. Normal mice aged either 9-10 months or 2-2.5 years and ApoE<sup>-/-</sup> mice aged 9-10 months were maintained for 1 month on a complete diet or a diet lacking folate and vitamin E and containing iron as a pro-oxidant, and additional groups received 0.5% AJC ad libitum in drinking water. Spectrophotometric assay of acetylcholine levels revealed a significant decline in homogenates of combined frontal cortex and hippocampus for all mice maintained on the deficient diet, and a prevention of this decline in mice maintained on the deficient diet when supplemented with AJC. These findings provide a likely mechanism by which consumption of antioxidant-rich foods such as apples can prevent the decline in cognitive performance that accompanies dietary and genetic deficiencies and aging.

### **J Nutr Health Aging. 2004;8(2):92-7.**

***Apple juice prevents oxidative stress and impaired cognitive performance caused by genetic and dietary deficiencies in mice.***

**Rogers EJ, Milhalik S, Orthiz D, Shea TB.**

#### **Abstract**

Increased oxidative stress contributes to the decline in cognitive performance during normal aging and in neurodegenerative conditions such as Alzheimer's disease. Dietary supplementation with fruits and vegetables that are high in antioxidant potential have in some cases compensated for dietary and/or genetic deficiencies that promote increased oxidative stress. Herein, we demonstrate that apple juice concentrate, administered ad libitum in drinking water, can compensate for the increased reactive oxygen species and decline in cognitive performance in maze trials observed when normal and transgenic mice lacking apolipoprotein E are deprived of folate and vitamin E. In addition, we demonstrate that this protective effect is not derived from the sugar content of the concentrate.

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### **J Agric Food Chem. 2008 Jul 9;56(13):4855-73.**

***Challenges for research on polyphenols from foods in Alzheimer's disease: bioavailability, metabolism, and cellular and molecular mechanisms.***

**Singh M, Arseneault M, Sanderson T, Murthy V, Ramassamy C.**

#### **Abstract**

Polyphenols are the most abundant antioxidants in diet. Indeed, fruits, vegetables, beverages (tea, wine, juices), plants, and some herbs are loaded with powerful antioxidant polyphenols. Despite their wide distribution, research on human health benefits truly began in the mid-1990s (Scalbert, A.; Johnson, I. T.; Saltmarsh, M. *Am. J. Clin. Nutr.* 2005, 81, S15S-217S). Phenolic compounds have been receiving increasing interest from consumers and manufacturers because numerous epidemiological studies have suggested associations between consumption of polyphenol-rich foods or beverages and the prevention of certain chronic diseases such as cancers and cardiovascular diseases (Manach, C.; Mazur, A.; Scalbert, A. *Curr. Opin. Lipidol.* 2005, 16, 77-84; Duthie, S. J. *Mol. Nutr. Food Res.* 2007, 51, 665-674). Furthermore, in the past 10 years, research on the neuroprotective effects of dietary polyphenols has developed considerably. These compounds are able to protect neuronal cells in various in vivo and in vitro models through different intracellular targets (Ramassamy, C. *Eur. J. Pharmacol.* 2006, 545, 51-64). However, it is not at all clear whether these compounds reach the brain in sufficient concentrations and in a biologically active form to exert beneficial effects. On the other hand, it has become clear that the mechanisms of action of these polyphenols go beyond their antioxidant activity and the attenuation of oxidative stress. Therefore, there is a need for more research on their intracellular and molecular targets as special pathways underlying distinct polyphenol-induced neuroprotection. The focus of this review is aimed at presenting the role of some polyphenols from fruits, vegetables, and beverages in neuroprotection and particularly in Alzheimer's disease and the research challenges in this area.

### **J Alzheimers Dis. 2005 Dec;8(3):283-7.**

***Apple juice concentrate prevents oxidative damage and impaired maze performance in aged mice.***

**Tchantchou F, Chan A, Kifle L, Ortiz D, Shea TB.**

#### **Abstract**

Oxidative stress contributes to age-related cognitive decline. In some instances, consumption of fruits and vegetables rich in antioxidant can provide superior protection than supplementation with purified antioxidants. Our prior studies have shown that supplementation with apple juice concentrate (AJC) alleviates oxidative damage and cognitive decline in a transgenic murine model compromised in endogenous antioxidant potential when challenged with a vitamin-deficient, oxidative stress-promoting diet. Herein, we demonstrate that AJC, administered in drinking water, is neuroprotective in normal, aged mice. Normal mice aged either 9-10 months or 2-2.5 years were maintained for 1 month on a complete diet or a diet lacking folate and vitamin E and containing iron as a pro-oxidant, after which oxidative damage was assayed by thiobarbituric acid-reactive substances and cognitive decline as assayed by performance in a standard Y-maze. Mice 9-12 months of age were unaffected by the deficient diet, while older mice demonstrated statistically-increased oxidative damage and poorer performance in a Y maze test. Supplementation with AJC prevented these neurodegenerative effects. These data are consistent

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with normal aged individuals being susceptible to neurodegeneration following dietary compromise such as folate deficiency, and a hastened onset of neurodegeneration in those individuals harboring a genetic risk factor such as ApoE deficiency. These findings also support the efficacy of antioxidant supplementation, including consumption of antioxidant-rich foods such as apples, in preventing the decline in cognitive performance that accompanies normal aging.

### **Curr Med Chem. 2011;18(8):1195-212.**

#### ***Neuroprotective actions of flavonoids.***

**Gutierrez-Merino C1, Lopez-Sanchez C, Lagoa R, Samhan-Arias AK, Bueno C, Garcia-Martinez V.**

#### **Abstract**

The experimental evidences accumulated during last years point out a relevant role of oxidative stress in neurodegeneration. As anti-cellular oxidative stress agents flavonoids can act either as direct chemical antioxidants, the classic view of flavonoids as antioxidants, or as modulators of enzymes and metabolic and signaling pathways leading to an overshoot of reactive oxygen species (ROS) formation, a more recently emerging concept. Flavonoids, a large family of natural antioxidants, undergo a significant hepatic metabolism leading to flavonoid-derived metabolites that are also bioactive as antioxidant agents. The development of more efficient flavonoid's based anti-oxidative stress therapies should also take into account their bioavailability in the brain using alternate administration protocols, and also that the major ROS triggering the cellular oxidative stress are not the same for all neurodegenerative insults and diseases. On these grounds, we have reviewed the reports on neuroprotection by different classes of flavonoids on cellular cultures and model animals. In addition, as they are now becoming valuable pharmacological drugs, due to their low toxicity, the reported adverse effects of flavonoids in model experimental animals and humans are briefly discussed.

### **Brain Res. 2014 Mar 25;1555:60-77.**

#### ***Neuroprotective effects of anthocyanin- and proanthocyanidin-rich extracts in cellular models of Parkinson's disease.***

**Strathearn KE, Yousef GG, Grace MH, Roy SL, Tambe MA, Ferruzzi MG, Wu QL, Simon JE, Lila MA, Rochet JC.**

#### **Abstract**

Neuropathological evidence indicates that dopaminergic cell death in Parkinson's disease (PD) involves impairment of mitochondrial complex I, oxidative stress, microglial activation, and the formation of Lewy bodies. Epidemiological findings suggest that the consumption of berries rich in anthocyanins and proanthocyanidins may reduce PD risk. In this study, we investigated whether extracts rich in anthocyanins, proanthocyanidins, or other polyphenols suppress the neurotoxic effects of rotenone in a primary cell culture model of PD. Dopaminergic cell death elicited by rotenone was suppressed by extracts prepared from blueberries, grape seed, hibiscus, blackcurrant, and Chinese mulberry. Extracts rich in anthocyanins and proanthocyanidins exhibited greater neuroprotective activity than extracts rich in other polyphenols, and a number of individual anthocyanins interfered with rotenone neurotoxicity. The blueberry and grape seed extracts rescued rotenone-induced defects in mitochondrial respiration

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in a dopaminergic cell line, and a purple basal extract attenuated nitrite release from microglial cells stimulated by lipopolysaccharide. These findings suggest that anthocyanin- and proanthocyanidin-rich botanical extracts may alleviate neurodegeneration in PD via enhancement of mitochondrial function.

### **Mol Nutr Food Res. 2013 Dec;57(12):2091-102.**

***Role of standardized grape polyphenol preparation as a novel treatment to improve synaptic plasticity through attenuation of features of metabolic syndrome in a mouse model.***

**Wang J, Tang C, Ferruzzi MG, Gong B, Song BJ, Janle EM, Chen TY, Cooper B, Varghese M, Cheng A, Freire D, Bilski A, Roman J, Nguyen T, Ho L, Talcott ST, Simon JE, Wu Q, Pasinetti GM.**

#### **Abstract**

##### SCOPE:

Metabolic syndrome has become an epidemic and poses tremendous burden on the health system. People with metabolic syndrome are more likely to experience cognitive decline. As obesity and sedentary lifestyles become more common, the development of early prevention strategies is critical. In this study, we explore the potential beneficial effects of a combinatory polyphenol preparation composed of grape seed extract, Concord purple grape juice extract, and resveratrol, referred to as standardized grape polyphenol preparation (SGP), on peripheral as well as brain dysfunction induced by metabolic syndrome.

##### METHODS AND RESULTS:

We found dietary fat content had minimal effect on absorption of metabolites of major polyphenols derived from SGP. Using a diet-induced animal model of metabolic syndrome (DIM), we found that brain functional connectivity and synaptic plasticity are compromised in the DIM mice. Treatment with SGP not only prevented peripheral metabolic abnormality but also improved brain synaptic plasticity.

##### CONCLUSION:

Our study demonstrated that SGP, comprised of multiple bioavailable and bioactive components targeting a wide range of metabolic syndrome related pathological features, provides greater global protection against peripheral and central nervous system dysfunctions and can be potentially developed as a novel prevention/treatment for improving brain connectivity and synaptic plasticity important for learning and memory.

### **Exp Gerontol. 2011 Nov;46(11):958-64.**

***Grape seed proanthocyanidin lowers brain oxidative stress in adult and middle-aged rats.***

**Asha Devi S, Sagar Chandrasekar BK, Manjula KR, Ishii N.**

#### **Abstract**

There is growing concern over the increasing instances of decline in cognitive abilities with aging in humans. The present study evaluated the benefits of the natural antioxidant, grape seed proanthocyanidin extract (GSPE) in treating the effects of age-related oxidative stress (OS) and accumulation of lipofuscin (LF) on the cognitive ability in rats. Female Wistar rats of 3- and 12-months of age received a daily oral supplement of GSPE until they attained 6- and 15-months of age. During this period, rats were tested

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for their cognitive ability. At the end of this period, blood glucose and markers of OS were assessed in the hippocampus. GSPE lowered blood glucose, lipid peroxidation, hydrogen peroxide level, and increased protein sulphhydryl (P-SH) content in the hippocampus. In addition, GSPE significantly improved cognitive performance in the two age groups. These results demonstrate that the extent of OS-related LF accumulation is reducible by GSPE. They also suggest a critical role for GSPE as a neuroprotectant in the hippocampus and in preventing cognitive loss with aging.

### **Med Sci Monit. 2006 Apr;12(4):BR124-9. Epub 2006 Mar 28.**

*Grape seed proanthocyanidin extract (GSPE) and antioxidant defense in the brain of adult rats.*

Devi A, Jolitha AB, Ishii N.

#### **Abstract**

##### BACKGROUND:

Proanthocyanidin (PA) is a naturally occurring antioxidant from grape seed extract. The present study aims at assessing the neuroprotective effects of grape seed proanthocyanidin (GSPE) on the cerebral cortex (CC), cerebellum (CB), and hippocampus (HC) in the adult rat brain.

##### MATERIAL/METHODS:

GSPE was orally administered at 25, 50, and 75 mg per kg body weight daily and for a total period of 9 weeks. Antioxidant enzymes (AOEs), superoxide dismutase (SOD), and catalase (CAT) were analyzed along with malondialdehyde (MDA) and protein carbonyl content (PCC) as markers of lipid peroxidation (LPO) and protein oxidation (PO). The cholinergic system was studied by analyzing choline acetyl transferase (ChAT) and acetylcholine esterase (AChE) activities along with acetylcholine content (ACh).

##### RESULTS:

The results obtained revealed an increased SOD activity in the 75-mg PA-supplemented animals, with a substantial decrease in MDA and PCC. The cholinergic neurotransmittary system analysis showed increased ChAT activity indicative of increased Ach content in the supplemented animals and the increase was more in the 75-mg PA group with a concomitant and moderate decrease in AChE activity. Regional changes were more with reference to HC.

##### CONCLUSIONS:

Our study shows that PA intake in moderately low quantity is effective in up-regulating the antioxidant defense mechanism by attenuating LPO and PO. Changes in the cholinergic system, however, indicate an increase in the ACh concentration with a moderate reduction in AChE activity, suggesting further that PA may have a potent role in enhancing cognition in older rats.

### **Eur J Neurol. 2013 Aug;20(8):1135-44.**

*Enzogenol for cognitive functioning in traumatic brain injury: a pilot placebo-controlled RCT.*

Theadom A, Mahon S, Barker-Collo S, McPherson K, Rush E, Vandal AC, Feigin VL.

#### **Abstract**

##### BACKGROUND AND PURPOSE:

Enzogenol, a flavonoid-rich extract from *Pinus radiata* bark with antioxidant and anti-inflammatory properties has been shown to improve working memory in healthy adults. In traumatic brain injury (TBI), oxidation and inflammation have been linked to poorer cognitive outcomes. Hence, this phase



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II, randomized controlled trial investigated safety, compliance and efficacy of Enzogenol for improving cognitive functioning in people following mild TBI.

### METHODS:

Sixty adults, who sustained a mild TBI, 3-12 months prior to recruitment, and who were experiencing persistent cognitive difficulties [Cognitive Failures Questionnaire (CFQ) score > 38], were randomized to receive Enzogenol (1000 mg/day) or matching placebo for 6 weeks. Subsequently, all participants received Enzogenol for a further 6 weeks, followed by placebo for 4 weeks. Compliance, side-effects, cognitive failures, working and episodic memory, post-concussive symptoms and mood were assessed at baseline, 6, 12 and 16 weeks. Simultaneous estimation of treatment effect and breakpoint was effected, with confidence intervals (CIs) obtained through a treatment-placebo balance-preserving bootstrap procedure.

### RESULTS:

Enzogenol was found to be safe and well tolerated. Trend and breakpoint analyses showed a significant reduction in cognitive failures after 6 weeks [mean CFQ score, 95% CI, Enzogenol versus placebo -6.9 (-10.8 to -4.1)]. Improvements in the frequency of self-reported cognitive failures were estimated to continue until week 11 before stabilizing. Other outcome measures showed some positive trends but no significant treatment effects.

### CONCLUSIONS:

Enzogenol supplementation is safe and well tolerated in people after mild TBI, and may improve cognitive functioning in this patient population. This study provides Class IIB evidence that Enzogenol is well tolerated and may reduce self-perceived cognitive failures in patients 3-12 months post-mild TBI.

## Phytother Res. 2008 Sep;22(9):1168-74.

*Improved cognitive performance after dietary supplementation with a Pinus radiata bark extract formulation.*

Pipingas A, Silberstein RB, Vitetta L, Rooy CV, Harris EV, Young JM, Frampton CM, Sali A, Nastasi J.

### Abstract

Dietary interventions may have the potential to counter age-related cognitive decline. Studies have demonstrated an improvement in age-related cognitive impairment in animals after supplementation with plant extracts containing flavonoids but there are few human studies. This double-blind, controlled study examined the effects on cognitive performance of a 5 week supplementation with Enzogenol Pinus radiata bark extract containing flavonoids, in 42 males aged 50-65 years, with a body mass index >25. Participants were supplemented for 5 weeks either with Enzogenol plus vitamin C, or with vitamin C only. A battery of computerized cognitive tests was administered, and cardiovascular and haematological parameters were assessed prior to and following supplementation. The speed of response for the spatial working memory and immediate recognition tasks improved after supplementation with Enzogenol plus vitamin C, whereas vitamin C alone showed no improvements. A trend in a reduction of systolic blood pressure was observed with Enzogenol plus vitamin C, but not with vitamin C alone. The blood safety parameters were unchanged. The findings suggest a beneficial effect of supplementation with Enzogenol on cognition in older individuals. Larger studies are needed to ascertain its potential as a preventive treatment for age-related cognitive decline.





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