Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Hachimijiogan

Evidence Summary

One clinical trial reported improved cognition in dementia patients with HJG, while another study showed mixed effects. It is typically prescribed to older people with kidney issues and poor circulation.

Neuroprotective Benefit: One clinical trial suggested cognitive benefits in dementia patients, while another trial showed mixed effects. In rodent studies, procognitive effects are accompanied by increased cholinergic activity and decreased inflammation.

Aging and related health concerns: A few clinical studies have suggested benefits for fatigue and peripheral arterial disease, but evidence from rigorously designed clinical trials are lacking. Studies in rodents suggest benefits in metabolic and lipid profiles.

Safety: HJG should not be taken by people with excess energy, flushing, or clapotement of the lower heart. Adverse events include rash, skin itching, loss of appetite, abdominal pain, palpitations, rush of blood to the head, and numbness of the tongue.

Availability: used clinically in Japan and China	**Dose**: The typical dose used in clinical studies is 2.5 g taken orally, 3 times per day.	**Ingredients:** rehmannia root, cornus fruit, dioscorea rhizome, alisma rhizome, poria sclerotium, moutan bark, cinnamon bark, and powdered processed aconite root
Half-life: depends on herb	**BBB**: depends on herb	
Clinical trials: The largest published study enrolled 69 mild Alzheimer's disease patients.	**Observational studies**: none available	

What is it?

Kampo medicine in Japan originates from traditional Chinese medicine, but the Japanese have created a unique system of diagnosis and therapy using a combination of herbs. Kampo medicine is approved by the Ministry of Health, Labor and Welfare and integrated in the Japanese healthcare system; it is covered by health insurance. Kampo medicine uses fixed combinations of herbs with standardized proportions and is under strict manufacturing and safety guidelines similar to those for drugs. More than half of Japanese physicians prescribe Kampo medicines.

Hachimijiogan (HJG), also known as Ba-Wei-Di-Huang-Wan in Chinese, is one of the most common herbal formulation in traditional Japanese, Chinese, and Korean medicines and has been used in many elderly patients for 2,000 years (Iwasaki et al., 2004). HJG is prescribed for the treatment of "kidney deficiency", but it is also used for symptoms common to older people, including lower back pain, nocturia, fatigue, muscle weakness, numbness, and coldness in the legs (Kainuma et al., 2022). It is also used to treat diabetes mellitus, hypertension, nephrotic syndrome, lack of energy, dysuria (pain during urination), pollakiuria (frequent urination), and poor eyesight in older people (Kubota et al., 2017). HJG is composed of 8 herbal components: rehmannia root, cornus fruit, dioscorea rhizome, alisma rhizome, poria sclerotium, moutan bark, cinnamon bark, and powdered processed aconite root. HJG contains many compounds including morroniside, (+)-catechin, loganin, paeoniflorin, benzoylmesaconine, cinnamic acid, benzoylpaeoniflorin, 16-ketoalisol A, paeonol, isoacteoside, cinnamaldehyde, and others (Hirotani et al., 2010).

Neuroprotective Benefit: One clinical trial suggested cognitive benefits in dementia patients, while another trial showed mixed effects. In rodent studies, procognitive effects are accompanied by increased cholinergic activity and decreased inflammation.

Types of evidence:

- 2 clinical trials in dementia patients
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

No studies have tested HJG treatment for the prevention of dementia or age-related cognitive decline.

Human research to suggest benefits to patients with dementia:

In an open-label randomized controlled trial of 69 patients with mild Alzheimer's disease, HJG treatment (2.5 g, 3 times daily, orally; TJ-7; Tsumura & Co., Tokyo, Japan) in addition to ongoing acetylcholinesterase inhibitor (AChEI) treatment for 6 months did not significantly improve cognitive function, measured by ADAS-Jcog, compared to the control group taking AChEI alone (Kainuma et al., 2022). The between-group difference in the ADAS-Jcog change from baseline to 6 months was 1.29 (p=0.293). Subgroup analyses showed a few trends, including in women, where the difference in the change from baseline to 3 and 6 months were 3.70 (p=0.059) and 2.90 (p=0.090), respectively, compared to the control group. Also, for patients over the age of 65, the difference at 3 months was 2.35 (p=0.099). The between-group differences from baseline to 3 and 6 months for male participants were negligible: -0.23 (p=0.873) and −0.66 (p=0.671), respectively. And patients under the age of 65 perform numerically worse with HJG, though differences were not statistically significant; the between-group difference from baseline to 3 and 6 months was -2.18 (p=0.307) and -0.79 (p=0.427), respectively. No significant effects of HJG were seen for functional activity (IADL score), apathy scale, or neuropsychiatric inventory questionnaire scores. While this clinical trial had a control group (AChEI only), it did not have a placebo control for the HJG, so a placebo effect cannot be ruled out. The study was also likely underpowered to detect differences in cognitive scores after 6 months of treatment.

In an older, smaller, but well-designed double-blind randomized controlled trial of 33 patients with mild to severe dementia (30 patients with AD and ischemic cerebrovascular disease, and 3 patients with pure AD), HJG treatment (2 g, 3 times daily, orally, after meals; Uchida Wakanyaku Co. Ltd, Tokyo, Japan) for

8 weeks significantly improved cognitive function measured by the MMSE (Iwasaki et al., 2004). The MMSE score significantly improved from 13.5 ± 8.5 to 16.3 ± 7.7 ($p<0.01$) in the HJG group, while a non-significant increase by 0.6 was observed in the placebo group (the placebo was made from black rice powder, sepia, and honey). Of the different cognitive functions, improvements in the serial 7s and three-word recall subscales were significantly improved with HJG ($p<0.05$). The function score (ADL score in the Barthel Index) also significantly improved with HJG treatment, from 61.8 ± 34.6 to 78.9 ± 21.1 ($p<0.01$), while no improvement was observed in the placebo group. Interestingly, 8 weeks after cessation of treatment, both the MMSE and the Barthel Index scores in the HJG group declined to baseline levels.

The pulsatility index in the internal carotid artery, as measured using Doppler sonography, significantly decreased in the HJG group (2.5 ± 1.7 to 1.9 ± 0.5; $p<0.05$), but not in the placebo group (2.4±2.2 to 2.0±1.3)(Iwasaki et al., 2004). The pulsatility index reflects vascular resistance, suggesting improved cerebrovascular resistance with HJG treatment, possibly through increasing cerebral blood flow. Blood pressure did not significantly change in either HJG or placebo groups (128.0±25.0 / 73.0±6.2 to 124.0±20.2 / 75.9±4.4 in the HJG group; 126.8±11.6 / 76.0±7.4 to 125.3±13.2 / 76.4±8.5 in the placebo group).

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

In a mouse model of cognitive dysfunction (induced by scopolamine, cycloheximide, or cerebral ischemia), HJG treatment (0.5 g/kg, orally) improved cognitive function, measured by the step-through passive avoidance task (Hirokawa et al., 1994). In a rat model of memory impairment (induced by scopolamine), HJG treatment (0.1 and 0.5 g/kg, orally) reduced the memory deficits, measured by the radial arm maze (Hirokawa et al., 1996). This reduction in cognitive deficits was accompanied by preservation of acetylcholine content in the frontal cortex. However, in the absence of scopolamine, HJG treatment did not affect cognitive function.

In a rat model of AD (intracerebroventricular Aβ injection with transient cerebral ischemia), HJG treatment (300 or 1,000 mg/kg, orally) rescued memory impairment measured by the Morris water maze and induced CREB phosphorylation/activation in the hippocampus (Kubota et al., 2017). In the same study, the authors demonstrated neurite outgrowth in PC12 cells with 6 herbal constituents of HJG (Rehmannia root, Dioscorea rhizome, Rhizoma Alismatis, Poria sclerotium, Moutan bark, and Cinnamon bark), though the strongest effect was seen with the HJG formulation (500 µg/ml). HJG treatment also induced neurotrophic effects through CREB-dependent mechanisms.

In a mouse model of accelerated aging (SAMP8 mice), HJG treatment for 13 weeks significantly reduced LPS-induced systemic inflammation (measured by IL-6 and MCP-1), but had no effect on tau expression (Ito et al., 2022).

In a mouse model of chronic fatigue syndrome (through repeated injections of Brucella abortus), HJG treatment for 4 weeks significantly reduced the expressions of pro-inflammatory cytokines (IL-1β, IL-6, and IFN-γ) in the hippocampus but not in the cortex (He et al., 2020). No effects of HJG were seen on oxidative stress markers (3-NT and 4-HNE) in the cortex or the hippocampus.

APOE4 interactions: Unknown.

Aging and related health concerns: A few clinical studies have suggested benefits for fatigue and peripheral arterial disease, but evidence from rigorously designed clinical trials are lacking. Studies in rodents suggest benefits in metabolic and lipid profiles.

Types of evidence:

- 4 clinical trials
- Numerous laboratory studies

Fatigue: EFFECTS LIKELY VARY

In an open-label clinical study of 20 patients with prolonged partial remitted major depressive disorder with fatigue or loss of energy, 8 patients who felt cold were treated with HJG (2.5 g, 3 times daily, orally; TJ-7; Tsumura & Co., Tokyo, Japan) for 4 weeks and the others were given Rokumigan (2.5 g, 3 times daily, orally; TJ-87; Tsumura & Co., Tokyo, Japan), a similar Kampo formula without 2 herbs present in HJG that are associated with generating warmth/heat (Yamada et al., 2005). Of the 20 patients, 6 patients were "much improved", 6 were "minimally improved", and 8 showed "no change" (non-responders) on the Clinical Global Impression Global Improvement scale. All responders (much or minimally improved) had "shofuku-fujin", which means tenderness or weakness of the lower abdomen. Of the 8 non-responders, 5 did not have "shofuku-fujin". In traditional Japanese (and Chinese) medicine, "shofuku-fujin" is one of the abdominal symptoms in people with fatigue or loss of energy. However, the exact biological and molecular mechanisms underlying the effects of HJG and rokumigan are not clearly elucidated. Because of the open-label design and lack of a placebo group, a placebo effect cannot be

ruled out. A larger, placebo-controlled, double-blind randomized trial is needed to validate these findings.

In aged rats, HJG treatment (chow containing 7% HJG; Tsumura Co., Ltd. Tokyo, Japan) for 10 weeks resulted in greater activity and spontaneous mobility during wheel running (87 ± 8 m/day compared to 53 ± 8 m/day in control group)(Ninomiya et al., 2001). Treated rats also maintained a significantly higher angle of retaining posture (45.0 ± 0.4 degrees) than the control group (41.3 ± 0.7 degrees) on the inclined screen.

Type 2 diabetes/ metabolic function: POTENTIAL BENEFIT BASED ON RODENT STUDIES
Mice fed an HJG-containing diet (3.8% in chow; Kotaro Pharmaceutical Co., Ltd, Osaka, Japan) for 4 weeks showed a reduction in adipocyte size with increased transcription of beige adipocyte-related genes in subcutaneous white adipose tissue (Kagawa et al., 2023). In mice fed a high-fat diet, HJG treatment (mixed in diet) for 4 weeks resulted in reduced weight gain, adipocyte hypertrophy, and liver steatosis, improved insulin sensitivity, and reduced circulating levels of leptin and FGF21 growth factor, without a change in food intake or oxygen consumption.

In a rat model of type 2 diabetes (type 2 diabetic Goto-Kakizaki rats), HJG treatment (pellets containing 1% HjG extract powder; Tsumura & Co., Ltd, Tokyo, Japan) for 14 weeks reduced hyperglycemia, increased insulin secretion, improved insulin response, and reduced plasma glucose levels after glucose administration (Hirotani et al., 2010). After 10 weeks of HJG treatment, plasma leptin levels also increased, suggesting better regulation of food intake.

In a different rat model of type 2 diabetes (induced by streptozotocin), HJG treatment (pellets containing 1% HJG extract powder; Tsumura & Co., Ltd, Tokyo, Japan) for 4 weeks markedly suppressed hyperglycemia and increased serum and pancreatic levels of insulin (Hirotani et al., 2007). However, this was not accompanied by an increase in the number of beta cells in the pancreatic Langerhans' islets. HJG treatment prevented the streptozotocin-induced increase in the expression of the glucose transporter 2 (GLUT2) protein, which is involved in glucose uptake and release in the liver. Together, HJG treatment increased insulin synthesis and release and normalized GLUT2 protein expression in the liver to suppress hyperglycemia. In the same rat model, HJG treatment (50, 100, 04 200 mg/kg, daily) for 10 days significantly decreased serum levels of glucose and glycosylated protein (Kim et al., 2004). HJG treatment also significantly reduced urinary protein levels and oxidative stress markers (free radicals, thiobarbituric acid-reactive substance levels in serum and hepatic and renal mitochondria).

In another rat model of type 2 diabetes (Otsuka Long-Evans Tokushima fatty rat), HJG treatment (50, 100, or 200 mg/kg, daily, orally; Tsumura Inc., Tokyo, Japan) for 32 weeks reduced hyperglycemia, urinary protein excretion, serum glycosylated protein levels, and renal advanced glycation end-prdocuts, and improved creatinine clearance levels (Yamabe and Yokozawa, 2006). HJG treatment also reduced oxidative stress markers (thiobarbituric acid-reactive substances) in renal mitochondria and inflammation markers (TGF-1β, inducible nitric oxide synthase, and cyclooxygenase-2). Together, the study suggests that HJG may have beneficial effects against the progression of diabetic nephropathy through attenuation of glucose toxicity and renal damage.

Cardiovascular function: UNCLEAR
In a double-blind randomized controlled trial of 33 patients with mild to severe dementia (30 patients with AD and ischemic cerebrovascular disease, and 3 patients with pure AD), HJG treatment (2 g, 3 times daily, orally, after meals; Uchida Wakanyaku Co. Ltd, Tokyo, Japan) for 8 weeks significantly decreased the pulsatility index in the internal carotid artery, as measured using Doppler sonograph (2.5 ± 1.7 to 1.9 ± 0.5; $p<0.05$), while no changes were observed in the placebo group (2.4±2.2 to 2.0±1.3)(Iwasaki et al., 2004). Blood pressure did not significantly change in either HJG or placebo groups (128.0±25.0 / 73.0±6.2 to 124.0±20.2 / 75.9±4.4 in the HJG group; 126.8±11.6 / 76.0±7.4 to 125.3±13.2 / 76.4±8.5 in the placebo group).

In an open-label clinical study of 24 aged people, treatment with HJG (Bai-wei-wan) for 7 months resulted in improvement in serum or plasma levels of total lipid, lipid peroxidation, and HDL-c (Yoshida et al., 1985). However, the full text of this study was inaccessible and therefore the study details could not be evaluated.

In aged rats and mice, HJG treatment decreased cholesterol and triglyceride levels, however the full text of this study was inaccessible, so details of the study results could not be evaluated (Haranaka et al., 1986).

Peripheral arterial disease: POTENTIAL BENEFIT
Intermittent claudication resulting from peripheral arterial disease can limit one's ability to walk and exercise. The first-line treatment for intermittent claudication is cilostazol; however, cilostazol cannot be used in patients with congestive heart failure. Based on a Kampo encyclopedia titled "Kampo Shinryo-Iten", HJG is recommended as the first-line Kampo medicine for the treatment of intermittent claudication resulting from arteriosclerosis. In an open-label uncontrolled study of 14 patients with peripheral arterial disease, HJG treatment (2.5 g, 3 times daily, orally, before or between meals; TH-7

from Tsumura & Co., Ltd, Tokyo, Japan) for 6 months improved the Walking Impairment Questionnaire (WIQ) subscores of pain, distance, and speed (Kawago et al., 2016). The median of the total score of WIQ improved significantly from 162.5 to 308.0 points. All patients showed improvement in the total WIQ score, and 7 out of 14 patients showed a remarkable improvement of more than 100 points on the WIQ. Absolute changes with HJG treatment exceeded those previously reported by cilostazol on all items of the WIQ. The authors discussed that the mechanisms behind the improvement with HJG may be attributed to the antiplatelet action of paeoniae moutan cortex and cinnamomic cortex, and analgesic action of aconiti rhizome. HJG treatment did not result in improvements in the ankle-brachial pressure index or the skin perfusion pressure, indicators of ischemia of the lower extremities.

Eye health: POTENTIAL BENEFIT
Studies suggest that a decrease in blood flow to the central retinal artery may underlie the progression of various eye diseases. In a clinical study of 12 healthy adults, administration of HJG increased systolic flow velocity, diastolic flow velocity, and mean flow velocity in the central retinal artery (Isobe et al., 2003). No changes were observed in vascular resistance after HJG administration, or blood flow velocities after placebo administration.

Peripheral neuropathy: NO BENEFIT
In a mouse model of peripheral neuropathy (induced by paclitaxel), HJG treatment (0.1-1.0 g/kg, orally) did not inhibit established allodynia but produced a slight inhibition of allodynia exacerbation (Andoh et al., 2014). However, treatment with a different Kampo forumulation, goshajinkigan, significantly inhibited established allodynia and allodynia exacerbation. Goshajinkigan is used for the treatment of pain and dysesthesia (unpleasant abnormal sensation) and has been tested for chemotherapy-induced peripheral neuropathy in cancer patients (Hoshino et al., 2018).

Safety: HJG should not be taken by people with excess energy, flushing, or clapotement of the lower heart. Adverse events include rash, skin itching, loss of appetite, abdominal pain, palpitations, rush of blood to the head, and numbness of the tongue.

Types of evidence:

- 4 clinical trials
- Numerous laboratory studies

In an open-label randomized controlled trial of 69 patients with mild Alzheimer's disease, HJG treatment (2.5 g, 3 times daily, orally; TJ-7; Tsumura & Co., Tokyo, Japan) in addition to ongoing acetylcholinesterase inhibitor (AChEI) treatment for 6 months resulted in one patient dropping out of the study due to interstitial pneumonia (Kainuma et al., 2022). This patient had lung disease at the start of the study, so the authors suggest that the adverse event was not due to HJG.

In a double-blind randomized controlled trial of 33 patients with mild to severe dementia, HJG treatment (2 g, 3 times daily, orally, after meals; Uchida Wakanyaku Co. Ltd, Tokyo, Japan) for 8 weeks did not cause adverse events such as stomach discomfort, diarrhea, eczema, or palpitations (Iwasaki et al., 2004). Three patients in the HJG group withdrew from the study during the observation period; one patient was transferred to another facility due to social reasons and two had adverse events (urinary tract infection and an upper respiratory tract infection).

In an open-label clinical study of 20 patients with prolonged partial remitted major depressive disorder with fatigue or loss of energy, 8 patients who felt cold were treated with HJG (2.5 g, 3 times daily, orally; TJ-7; Tsumura & Co., Tokyo, Japan) for 4 weeks and the others were given Rokumigan (2.5 g, 3 times daily, orally; TJ-87; Tsumura & Co., Tokyo, Japan), a similar Kampo formula without 2 herbs present in HJG that are associated with generating warmth/heat (Yamada et al., 2005). No adverse events were experienced in those taking HJG.

In an open-label uncontrolled study of 14 patients with peripheral arterial disease, HJG treatment (2.5 g, 3 times daily, orally, before or between meals; TJ-7 from Tsumura & Co., Ltd, Tokyo, Japan) for 6 months resulted in 5 patients dropping out (Kawago et al., 2016). One patient had lung surgery 2 months after starting HJG treatment, then experienced gastrointestinal symptoms at 4 months. At that time, the patient demonstrated air-fluid level formation at the stomach on upright abdominal X-rays and clapotement of the lower heart (splashing sound at the epigastric region when tapped) for the first time. The other patient got a rash, which, based on a comment from a dermatologist, the cause of the rash was unlikely to be due to HJG; however, the patient discontinued participation in the study. The remaining 3 patients requested discontinuation of HJG due to progression of other diseases (cardiac insufficiency, inguinal hernia strangulation, aggravation of low back pain). HJG is contraindicated in patients with clapotement of the lower heart, so patients with this condition were excluded from enrollment.

HJG has occasionally caused adverse events including hot flashes and a burning sensation, probably induced by Aconiti tuber and Cinnamomi cortex (Yamada et al., 2005). Rokumigan, which does not contain these 2 herbs, is available for patients who do not have a complaint of feeling cold.

Based on product information sheets for HJG, possible adverse reactions may include rash, skin redness, itching, loss of appetite, gastric distress, abdominal pain, palpitations, rush of blood to the head, cheilitis (lip inflammation), and numbness of the tongue (Tsumura & Co information sheet for customers).

Drug interactions: Drug interactions have not been well-studied or documented for HJG.

Sources and dosing:

HJG is manufactured by various pharmaceutical companies in Japan. One of the most commonly tested HJG in clinical trials is the TJ-7 formulation from Tsumura & Co. Ltd, Tokyo, Japan. HJG is manufactured in compliance with Japanese Good Manufacturing Practice (GMP) that ensures quality control (Kainuma et al., 2022). The daily dose of HJG extract (7.5 g) is derived from 8 dried herbal components: Rehmannia Root (6.0 g), Cornus Fruit (3.0 g), Dioscorea Rhizome (3.0 g), Alisma Rhizome (3.0 g), Poria Sclerotium (3.0 g), Moutan Bark (2.5 g), Cinnamon Bark (1.0 g), and Powdered Processed Aconite Root (0.5 g). These herbs are mixed together, extracted using hot water, and made into powder by spray drying. HJG has most frequently been tested in clinical trials at a 2.5 g dose, 3 times daily, orally, with warm water.

Research underway:

No clinical trials testing HJG are currently underway, based on ClinicalTrials.gov and the Japanese registry, UMIN Clinical Trials Registry.

Search terms:

Pubmed, Google:

- Hachimijiogan
- Ba Wei Di Huang Wan

Websites visited for Hachimijiogan, Ba Wei Di Huang Wan:

- Clinicaltrials.gov (0)
- UMIN.ac.jp Clinical Trials Registry (0)
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com (0)
- DrugBank.ca (0)