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.

Kamikihito (also known as kami-guibi-tang and jia-wei-gui-pi-tang)

Evidence Summary

Kamikihito may improve function and cognition in people with mild cognitive impairment or dementia, though larger placebo-controlled studies are needed. Adverse events are mostly gastrointestinal issues.

Neuroprotective Benefit: Kamikihito improved function and/or cognition in people with MCI, AD, or vascular dementia, but all studies have been small, and most were not placebo-controlled. Kamikihito also lowered incidence of delirium in ICU patients.

Aging and related health concerns: In two small studies in cancer patients, kamikihito treatment improved treatment side effects such as fatigue and insomnia. Larger, randomized controlled trials are needed to validate these findings.

Safety: Unlike herbs in the US, kamikihito is manufactured under strict quality control in Japan as medicine. Common side effects include nausea, abdominal pain, diarrhea, and rash. Rare adverse events include low potassium levels and increased blood pressure.

Availability: used clinically in Japan, South Korea, and China	**Dose**: In clinical trials, typically 3 grams per pack of granules were dissolved in water and taken 3 times a day.	**Chemical formula:** N/A **MW**: N/A
Common/preferred brand: different brands have been used across clinical trials (e.g., Tsumura, Kracie, and Kyoung Bang Pharmaceutical)		
Half-life: depends on herb	**BBB**: depends on herb	
Clinical trials: Most studies have been small (10-35 subjects), and many have been open-label studies.	**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.

Kamikihito is a type of Kampo medicine used clinically to treat anxiety, insomnia, depression, amnesia, hot flashes, and gastritis. Kamikihito is composed of 14 herbs: Astragalus root, Bupleurum root, Jujube seed, Atractylodes Lancea rhizome, Panax Ginseng, Poria Sclerotium, Longan Aril, Polygala root, Gardenia fruit, Jujube, Japanese Angelica root, Glycyrrhiza, Ginger, and Saussurea root. The anxiolytic effects of kamikihito are likely due to changes in the levels of GABA-A and serotonin 5HT-2A receptors (Yamada et al., 1994; Ishihara et al., 1994).

Kihito is another kind of Kampo medicine with 12 out of the 14 herbs included in Kamikihito. Kihito is composed of: Astragalus root, Jujube seed, Atractylodes rhizome, Panax Ginseng, Poria Sclerotium, Longan Aril, Polygala root, Jujube, Japanese Angelica root, Glycyrrhiza, Ginger, and Saussurea root. Kihito has been used for patients with insomnia, forgetfulness, palpitations, anxiety, fatigue, poor appetite, depression, gastritis, short menstrual cycle, and spotting between periods.

Kamikihito is called kami-guibi-tang in Korea and jia-wei-gui-pi-tang in China.

Neuroprotective Benefit: Kamikihito improved function and/or cognition in people with MCI, AD, or vascular dementia, but all studies have been small, and most were not placebo-controlled. Kamikihito also lowered incidence of delirium in ICU patients.

Types of evidence:

- 1 double-blind randomized placebo-controlled pilot study in amnestic MCI patients
- 3 clinical trials in dementia patients in Japan
- 1 open-label crossover trial in Alzheimer's patients
- 1 clinical study in ICU patients with cardiovascular disease
- Numerous laboratory studies

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

In a single-center randomized double-blind placebo-controlled pilot study in 30 patients with amnestic mild cognitive impairment, treatment with kami-guibi-tang granules (3 g/pack, 3 times per day, dissolved in hot water; Kyoung Bang Pharmaceutical Co. Ltd) for 24 weeks did not significantly improve the Seoul Neuropsychological Screening Battery Dementia version (SNSB-D) score compared to placebo (Shin et al., 2021). The SNSB-D is a comprehensive test that is sensitive in monitoring changes in cognitive function and has been used as a tool to discriminate between mild cognitive impairment, Alzheimer's disease, and normal aging (Ahn et al., 2010). In the kami-guibi-tang group, the total SNSB-D score increased significantly from baseline from 176.00 (±24.76) to 198.47 (±31.29) points at 24 weeks ($p<0.001$), while no improvement was seen in the placebo group ($p=0.143$); and no statistically significant difference was found between the groups (Shin et al., 2021). There was also no significant difference between groups on the memory domain score at 24 weeks.

For the Seoul Verbal Learning Test (SVLT), recall test score increased from 17.5 to 24.5 points; the Rey Complex Figure Test (RCFT) recall test score increased from 20.00 to 29.91 points; and the RCFT recognition score increased from 5.9 to 7.6 points after 24 weeks of kami-guibi-tang treatment ($p=0.003$, $p<0.001$, and $p=0.002$, respectively)(Shin et al., 2021). However, changes from baseline were not significant in the placebo group, and there were no significant differences in scores between the two groups at 24 weeks.

The Clinical Dementia Rating sum-of-boxes (CDR-SB) score improved significantly from 1.53 (±0.64) points to 1.13 (±0.62) points after kami-guibi-tang treatment ($p=0.010$), while it worsened from 1.61 (±0.88) points to 1.75 (±0.94) points in the placebo group (Shin et al., 2021). There was a significant

difference between the two groups (p=0.045). After 24 weeks of intervention, 31.25% of the kami-guibi-tang group had a reversion of the CDR score from 0.5 ("questionable dementia") to 0 point ("no dementia"), while 14.29% of the placebo group had a reversion. However, the reversion rate was not significantly different between the two groups (p=0.399).

Other scores (Korean MMSE, Global Deterioration Score, Activities of Daily Living, Geriatric Depression Scale) were not affected by the intervention and there were no significant differences between kami-guibi-tang treatment and placebo groups (Shin et al., 2021).

In the same clinical trial, different brain parameters were examined, including MRI, brain metabolites, and cerebral blood flow (Cho et al., 2021). Cerebral blood flow values were significantly lower after treatment in the hippocampus for both the kami-guibi-tang and placebo groups, and at the fusiform gyrus for the kami-guibi-tang group. The absolute cerebral blood flow difference before and after treatment in the fusiform gyrus was significantly lower in the kami-guibi-tang group compared to placebo (p=0.024). The authors speculate that the lower cerebral blood flow could be due to a compensatory response to maintain memory function, referencing some studies where higher cerebral blood flow was associated with cognitive impairment (Bangen et al., 2017). Measures of brain metabolites were not significantly altered with kami-guibi-tang treatment compared to placebo (GABA/creatine, glutamate complex/creatine, N-acetylaspartate/creatine, choline/creatine, and myo-inositol/creatine ratios)(Cho et al., 2021).

In a clinical study of 59 ICU patients with cardiovascular disease, addition of acupuncture treatment combined with kamikihito (3 times per day, orally) to conventional care for one week was associated with a significantly lower incidence of delirium (6.6%) compared to the control group that received only conventional care (37.9%)(Matsumoto-Miyazaki et al., 2017). Sedative drugs and non-pharmacological approaches for aggressive behavior were used less in the acupuncture plus kamikihito group compared to the conventional care alone group. Future studies with a randomized controlled design are needed to confirm these initial findings.

Human research to suggest benefits to patients with dementia:
Based on a 2015 review on kamikihito (written in Japanese), there had been 3 clinical trials testing kamikihito or kihito in dementia patients (Tohda et al., 2015).

In a controlled study (not placebo-controlled; controls received no treatment) of 40 Alzheimer's patients, 20 patients received 4.5 g of kihito daily for 3 months while the other 20 patients received no

kihito. At baseline, mean Mini-Mental State Examination (MMSE) scores were 17.6 for both groups, but at 3 months the kihito-treated group increased their scores by 1.65 points on average. The untreated group had an average decrease of 0.3 points at 3 months.

In an open-label study of 6 Alzheimer's patients and 6 vascular dementia patients, kamikihito (7.5 g/day) treatment for 8 weeks significantly improved cognitive function, as measured by the Hasegawa Dementia Rating Scale, when compared to baseline (no placebo controls). Average scores at baseline, 4 weeks, and 8 weeks were 12.8 points, 14.2 points, and 15.9 points, respectively, with the 8-week mark being statistically different from baseline. Scores of daily living were also significantly improved at 4 and 8 weeks.

In another study in Alzheimer's patients, kihito treatment 3 times daily for 3 months improved orientation, attention, and language, as measured by MMSE, though no details on the size of the study or the dosages were noted in the review (and the original article was inaccessible).

More recently, an open-label crossover clinical trial of 10 Alzheimer's patients reported that kihito treatment (2.5 g of kihito extract 3 times per day; TJ-65 from Tsumura, Tokyo, Japan) combined with a cholinesterase inhibitor for 16 weeks increased cognitive scores (MMSE-J scores) compared to the 16-week period when cholinesterase inhibitor alone was taken (Watari et al., 2019). A 1.8-point reduction was seen in the MMSE-J score during the cholinesterase inhibitor-alone treatment period, whereas the score slightly increased during the kihito treatment period. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS-J) test scores were slightly better during the kihito treatment period compared with the cholinesterase inhibitor alone period, but no statistically significant differences were observed. A 2.7-point reduction was seen during the cholinesterase inhibitor-alone period, whereas there was less decline during the kihito treatment period.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
Kamikihito treatment improves cognitive function in normal mice (Watari et al., 2015) and in a mouse model of Alzheimer's disease (5xFAD; Tohda et al., 2011). In a rat model of chronic stress (chronic restraint stress), kamikihito treatment (300 or 1,000 mg/kg; Tsumura, #TJ-137) for 21 days rescued the effects of stress, including changes in body weight and increased corticosterone levels (Adachi et al., 2021). Neurogenesis was significantly suppressed (by approximately 60%) with chronic stress, but kamikihito treatment restored it to levels comparable to unstressed animals. In a rat model of acute stress (acute immobilization stress), pretreatment with kamikihito (1 or 3% in food; Tsumura, #TJ-137) for 7 days significantly increased adrenocorticotrophic hormone (ACTH) and corticosterone levels

following acute stress, and increased cerebral spinal fluid levels of oxytocin (Tsukada et al., 2021). In aged mice, chronic kamikihito treatment (1% w/v in drinking water) improved cognitive functions (place learning acquisition, behavioral flexibility) compared to age-matched controls (Oizumi et al., 2020). Kamikihito treatment also improved effort-based decision making in both young and aged mice.

Similarly, kihito treatment improves cognitive function in a mouse model of accelerated aging (Nishizawa et al., 1990), a mouse model of Alzheimer's (Tohda et al., 2008), and in cognitively impaired rats (injected with scopolamine or THC; Egashira et al., 2007). Based on the similarity of results, it is possible that the cognitive-enhancing ingredients may lie in the 12 out of the 14 common herbs. A study has compared kamikihito with kami-guibi-tang (Korean version of kamikihito, with all of the same herbs) and reported equivalent memory-enhancing effects in normal mice (Watari et al., 2015). No studies have directly compared kamikihito with kihito on cognitive effects.

There are several potential mechanisms of neuroprotection with kamikihito or kihito. In aged rats, kamikihito significantly increases the density of muscarinic acetylcholine receptors and the activity of choline acetyltransferase (ChAT), an enzyme that increases acetylcholine levels in the brain (Egashira et al., 1991). Kamikihito also increases the activity of protein phosphatase 2A (PP2A), which is an enzyme that dephosphorylates tau (Watari et al., 2014). It also prevents axonal degeneration induced by Aβ in cultured neurons. In Alzheimer's model mice (5xFAD), Kamikihito treatment reduced the number of amyloid plaques in the frontal cortex and hippocampus (Tohda et al., 2011). In cultured cortical neurons, kamikihito induced axonal outgrowth (Tohda et al., 2011) and this axonal extension property may be due in part to a chemical (20-O-β-D-glucopyranosyl-20(S)-protopanaxadiol) derived from Ginseng Radix, one of the components of kamikihito and kihito. Kihito also increases the density of neurites, synapses, and myelin in the brains of Alzheimer's mice (injected with Aβ)(Tohda et al., 2008).

APOE4 interactions: Unknown.

Aging and related health concerns: In two small studies in cancer patients, kamikihito treatment improved treatment side effects such as fatigue and insomnia. Larger, randomized controlled trials are needed to validate these findings.

Types of evidence:

- 1 controlled trial in women undergoing treatment for gynecological malignant tumors
- 1 open-label study in prostate cancer or metastatic renal cell cancer patients
- A few laboratory studies

Cancer: IMPROVES SIDE EFFECTS FROM TREATMENTS
In a randomized parallel group trial of 33 patients who had menopausal symptoms while undergoing treatment for gynecological malignant tumors, treatment with kamikihito (7.5 g, twice daily; Kracie Pharma Ltd., Tokyo, Japan) was compared with another Kampo formulation, kamishoyosan (6.0 g, twice daily; Kracie Pharma Ltd.)(Yoshimura et al., 2018). After 8 weeks of treatment, the Kupperman Menopausal Index (KI) scores significantly decreased compared with baseline in both treatment groups, with no statistically significant difference between the kamikihito and kamishoyosan treatments. Both kamikihito and kamishoyosan were effective for insomnia, vertigo, and palpitation. Kamishoyosan also improved vasomotor symptoms and arthralgia/myalgia. Because there was no placebo control, some of the benefits could be due to placebo effects.

In an open-label clinical study of 35 prostate cancer or metastatic renal cell cancer patients treated with hormone or antitumor therapy, kamikihito treatment (2.5 g, 3 times daily before or between meals; Tsumura & Co., Tokyo, Japan) for 12 weeks showed improved scores for fatigue, depression, and sleepiness (Tamada et al., 2018). Fatigue score (measured by the Chalder fatigue scale) before kamikihito treatment was 42.9 ± 16.8 (normal range < 16), but after 4 weeks of kamikihito treatment, there was a statistically significant improvement (24.5 ± 8.5), which persisted to 12 weeks. The Center for Epidemiologic Studies Depression scale and the Epworth sleepiness scale (normal range < 11) scores were significantly reduced below the baseline. Kamikihito treatment also improved autonomic nervous system balance (e.g., increased parasympathetic activity), reduced serum levels of reactive oxygen species, and increased antioxidant potential. However, due to the open-label design of the study, observed improvements could be due in part to placebo effects.

Inflammation: MIXED. In a mouse model of inflammation (injected with bacterial endotoxin lipopolysaccharide; LPS), kamikihito treatment (10 ml/kg of 27% herbal mixture injected orally) ameliorated the sickness behavior and prevented cognitive deficits, as measured by novel object

exploration, social interaction, and forced swim test (Araki et al., 2016). However, kamikihito did not affect mRNA expression of inflammatory markers, such as COX2, IL-1β, and IL-6.

Ischemia: BENEFIT. In mice and gerbils that received kamikihito pretreatment (2g/kg/day, oral) for 5 days followed by carotid artery occlusion, survival was prolonged to 40 minutes compared to 25 minutes in untreated animals (Nishizawa et al., 1994). Kamikihito also prolonged survival time in mice injected with the excitotoxic NMDA, from 100 sec (control) to 130-160 sec in treated mice. Although benefits are seen with kamikihito treatment, the experimental protocol is drastic as it results in rapid death of the animals. Also, no mechanisms are explored. It is difficult to extrapolate these results to how kamikihito may help ischemia patients.

Safety: Unlike herbs in the US, kamikihito is manufactured under strict quality control in Japan as medicine. Common side effects include nausea, abdominal pain, diarrhea, and rash. Rare adverse events include low potassium levels and increased blood pressure.

Types of evidence:

- 1 double-blind randomized placebo-controlled pilot study in amnestic MCI patients
- 1 controlled trial in women undergoing treatment for gynecological malignant tumors
- 1 open-label crossover trial in Alzheimer's patients
- 1 clinical study in ICU patients with cardiovascular disease
- 1 case study of lung injury
- Japanese Adverse Drug Event Report database from Pharmaceuticals and Medical Devices Agency in Japan (PMDA)
- Leaflets of kamikihito preparation
- Review articles

Although the pharmaceutical (prescription) grade versions are approved by the Japanese Ministry of Health, Labor and Welfare, safety of kamikihito has not been investigated thoroughly in clinical trials, so the incidence of adverse reactions is unknown. Adverse drug reactions are monitored by the Pharmaceuticals and Medical Devices Agency in Japan (pmda.go.jp). Since 2012, the Japanese Adverse Drug Event Report database became available online, allowing consumers to view all reported cases of adverse drug events from 2004. There have been no reported cases of adverse drug events related to kamikihito. Safety problems due to poor quality are likely uncommon as the prescription-grade Kampo medicines undergo strict quality control (Teng et al., 2016).

Common side effects for kamikihito (and kihito) include nausea, abdominal pain, decreased appetite, diarrhea, and rash (Tsumura & Co leaflet). Although rarely reported, low potassium levels, increased blood pressure from fluid retention, and myopathy (resulting from low potassium levels) have also been associated with kamikihito. Glycyrrhiza is the herb associated with potassium-lowering effects, as it accelerates potassium excretion via the renal tubules. Patients with anorexia, nausea, vomiting, eczema and dermatitis may experience worsening of symptoms.

In a single-center randomized double-blind placebo-controlled pilot study in 30 patients with amnestic mild cognitive impairment, treatment with kami-guibi-tang granules (3 g/pack, 3 times per day, dissolved in hot water; Kyoung Bang Pharmaceutical Co. Ltd) for 24 weeks did not result in adverse events that were different in frequency compared to the placebo group (Shin et al., 2021). There were no abnormalities in vital signs, blood test (BUN, Cr, AST, ALT, Na, K, Cl, CPK, LDH, and glucose), ECG, and brain MRI findings after the intervention. Approximately 11.8% of the kami-guibi-tang group and 12.5% of the placebo group reported adverse events. In the kami-guibi-tang group, one participant had temporomandibular joint pain and one had mild dyspepsia. These symptoms appeared after kami-guibi-tang treatment for more than 12 weeks and subsided spontaneously within 2 weeks. In the placebo group, one patient had heartburn and another developed gastric cancer. No links were found between these adverse events and the study drug.

An open-label crossover clinical trial of 10 Alzheimer's patients reported that kihito treatment (2.5 g of kihito extract 3 times per day; TJ-65 from Tsumura, Tokyo, Japan) combined with a cholinesterase inhibitor for 16 weeks did not result in side effects or adverse events during safety assessment visits (Watari et al., 2019).

In a clinical study of 59 ICU patients with cardiovascular disease, addition of acupuncture treatment combined with kamikihito (3 times per day, orally) to conventional care for one week did not result in any serious adverse events, though the full text was inaccessible and the types and frequencies of adverse events could not be evaluated (Matsumoto-Miyazaki et al., 2017).

In a randomized parallel group trial of 33 patients who had menopausal symptoms while undergoing treatment for gynecological malignant tumors, treatment with kamikihito (7.5 g, twice daily; Kracie Pharma Ltd., Tokyo, Japan) was compared with another Kampo formulation, and adverse events were reported in 2 patients (1 diarrhea and 1 joint pain)(Yoshimura et al., 2018). In both cases, patients discontinued treatment. The causal relationship between kamikihito and adverse events were not clear.

In a case study, lung injury was reported in an 89-year-old Japanese male who had hypertension, arrhythmia, and chronic heart failure (Tahara et al., 2019). The patient experienced tinnitus and kamikihito was prescribed, but the patient experienced dry cough and breathing difficulty. Chest computed tomography showed patchy consolidations and ground-glass opacities in the right upper lobe of the lungs, and ground-glass opacities in the bilateral lower lobes. A drug lymphocyte stimulation test (DLST) for kamikihito was positive. Thus, authors noted that kamikihito-induced lung injury was most likely, and treatment with prednisolone (50 mg/day) was started. Respiratory symptoms and chest radiographic findings improved rapidly after prednisolone treatment.

Sources and dosing: Kamikihito appears to not be available in the US, though individual herbs are available as supplements. Kamikihito is treated as a drug in Japan (as all Kampo formulations are) and sold by several pharmaceutical companies: Tsumura, Kracie, Tatebayashi, Oosugi, and Taikoseido. Kamikihito often comes in 2.5g packets of dried extract granules and the recommended dose is 7.5 g/day orally (containing 5.0 g of dried extract) in 2 or 3 divided doses before or between meals. The kamikihito granules (7.5 g) from Tsumura contains 5.0 g of dried extract from the following mix: astragalus root (3.0 g), bupleurum root (3.0 g), jujube seed (3.0 g), astractylodes lancea rhizome (3.0 g), ginseng (3.0 g), poria sclerotium (3.0 g), longan aril (3.0 g), polygala root (2.0 g), gardenia fruit (2.0 g), jujube (2.0 g), Japanese angelica root (2.0 g), glycyrrhiza (1.0 g), ginger (1.0 g), and saussurea root (1.0 g).
These extracts are ingested and washed down with water. Over-the-counter formulations are not as tightly regulated and tend to have lower amounts of the active ingredients.

Research underway: No clinical trials testing kamikihito are underway, based on ClinicalTrials.gov and the UMIN.ac.jp (clinical trial registry in Japan).

Search terms:
Pubmed, Google: Kamikihito, Kihito, kami-buigi-tang, Jia Wei Gui Pi Tang

Clinicaltrials.gov, UMIN.ac.jp (Japanese clinical trial registry): Kamikihito, Kihito

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If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit Cognitive Vitality's Rating page.