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

Evidence Summary

Kamikihito may slow cognitive decline in dementia patients, though long-term safety is undocumented.

Neuroprotective Benefit: Small clinical trials in Japan have shown benefits in cognitive function in patients with Alzheimer's and vascular dementia.

Aging and related health concerns: A few preclinical studies suggest protection in models of inflammation and ischemia, but impossible to extrapolate to humans.

Safety: Safety data from long-term clinical trials are lacking, though unlike herbs in the US, Kamikihito is manufactured under strict quality control. Rare adverse effects include low potassium levels and increased blood pressure due to fluid retention.

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 kind 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, 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, 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.

Neuroprotective Benefit: Small clinical trials in Japan have shown benefits in cognitive function in patients with Alzheimer's and vascular dementia.

Types of evidence:

- 3 clinical trials in dementia patients in Japan
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function? None available.

Human research to suggest benefits to patients with dementia. All of the available evidence is published in Japanese journals and the original research articles were not accessible in the US (archived in Japanese medical schools).

Based on a 2015 review on Kamikihito (written in Japanese), there have been 3 clinical trials 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).

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). 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: A few preclinical studies suggest protection in models of inflammation and ischemia, but impossible to extrapolate to humans.

Types of evidence:

- A few laboratory studies

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 PRECLINICAL MODELS. 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: Safety data from long-term clinical trials are lacking, though unlike herbs in the US, Kamikihito is manufactured under strict quality control. Rare adverse effects include low potassium levels and increased blood pressure due to fluid retention.

Types of evidence:

- Japanese Adverse Drug Event Report database from Pharmaceuticals and Medical Devices Agency in Japan (PMDA)
- Leaflets of Kamikihito preparation
- Review articles

Details: 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). In 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.

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. 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: There is a clinical trial in Japan testing the effects of Kihito on cognitive functions in Alzheimer's disease patients (R000027079). Although it is a randomized trial, it is not placebo-controlled; patients will either receive standard treatment (cholinesterase inhibitor) alone or in combination with Kihito for 16 weeks. This trial is currently recruiting participants by invitation and is scheduled to be completed in March 2019. Another clinical trial will test the safety and efficacy of

Kamikihito for the treatment of anxiety and insomnia in prostate cancer patients receiving hormone therapy (R000025988).

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