*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.*

# Kamiuntanto

**Evidence Summary**

Small clinical trials suggest KUT may improve some cognitive functions in Alzheimer's patients, but there have not been any large rigorously designed placebo-controlled clinical trials to date.

**Neuroprotective Benefit:** While some cognitive improvements have been observed with KUT, all clinical trials to date have used open-label designs with no placebo controls. Studies in rodent models suggest KUT increases ChAT activity and NGF levels.

**Aging and related health concerns:** Studies in mouse models of aging and memory impairment reported higher survival rates with KUT treatment. No studies in humans have evaluated whether KUT increases lifespan or decreases age-related diseases.

**Safety:** While KUT has a long history of use in Japan, there have been no large, randomized placebo-controlled trials testing the long-term safety of KUT. Rarely, Glycyrrhiza radix can lower K+ levels and increase blood pressure and edema.

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| **Availability**: used clinically in Japan | **Dose**: Typical commercial products come in packets of dried herbal extract; each packet contains 2.0 g of dried herbal extract, which is taken 2 or 3 times per day, orally. | **Herbal components:** Pinelliae tuber, Hoelen, Aurantii Nobilis Pericarpium, Banbusae Caulis, Polygalae Radix, Glycyrrhizae Radix, Scrophulariae Radix, Aurantii Fructus Immaturus, Zizyphi Semen, Rehmanniae Radix, Zizyphi Fructus, Ginseng Radix, and Zingiberis Rhizoma |
| **Half-life**: depends on compounds/herbs | **BBB**: some compounds are likely penetrant | |
| **Clinical trials**: The largest completed clinical trial was an open-label controlled trial of 52 Alzheimer's patients. | **Observational studies**: There are some published case studies but no large observational studies. | |

**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.

Kamiuntanto (加味温胆湯; KUT) is a type of Kampo medicine used clinically to treat insomnia, anxiety/depression, and neurological diseases in people who have low-to-medium physical strength and a sensitive gastrointestinal system. KUT has been studied in a few clinical trials in Alzheimer's patients (Suzuki et al., 2001; Arai et al., 2000; Maruyama et al., 2006). KUT consists of 13 herbs: Pinelliae tuber, Hoelen, Aurantii Nobilis Pericarpium, Banbusae Caulis, Polygalae Radix, Glycyrrhizae Radix, Scrophulariae Radix, Aurantii Fructus Immaturus, Zizyphi Semen, Rehmanniae Radix, Zizyphi Fructus, Ginseng Radix, and Zingiberis Rhizoma. Studies in rodent models suggest that the neuroprotective effects of KUT are mediated by increased activities of the choline acetyltransferase (ChAT; an enzyme essential for synthesizing the neurotransmitter acetylcholine) and nerve growth factors (Yabe et al., 1996).

**Neuroprotective Benefit:** While some cognitive improvements have been observed with KUT, all clinical trials to date have used open-label designs with no placebo controls. Studies in rodent models suggest KUT increases ChAT activity and NGF levels.

*Types of evidence:*

- 3 controlled clinical trials
- 1 case studies
- Numerous laboratory studies

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

There have not been any clinical trials or observational studies that have tested the effects of KUT for prevention of dementia or age-related cognitive decline.

One study reported 4 cases of dysthymic disorder and general malaise who were successfully treated with KUT (Kogure et al., 2010). Dysthymic disorder is a disabling psychiatric disorder characterized by mild but persistent depressive symptoms, fatigue, and sleeplessness, lasting more than 2 years.

- Case 1: A 63-year-old man requested Kampo medicine for dysthymic disorder with sleeplessness and malaise that had persisted for about 5 years despite treatment with antidepressants (trazodone, estazolam, sulpirid). He worked at a bakery as a full-time employee but had been taking time off of work several days a month due to fatigue. Treatment with Kamikihito for 4 weeks failed to improve his symptoms. KUT was therefore administered in addition to antidepressants. After KUT therapy for 12 weeks, sleeplessness and malaise improved. The patient was able to commute to work every day and the improvement in social activities had continued for 3 years with KUT.
- Case 2: A 62-year-old woman requested Kampo medicine for general malaise and lack of volition that had persisted for 2 years despite conventional therapy (zolpidem, brotizolam, etizolam). She was a housewife and was barely able to perform housework. Saikokeishikankyoto therapy in addition to conventional therapy for 4 months failed to improve her symptoms. The Kampo formula was changed to KUT. Dysthymia, consisting of general malaise and depressive symptoms, was reduced by 80% after KUT therapy for about 4 months, along with the occasional use of Kousosan (TJ-70, 2.5 g, Tsumura, Japan) to relieve her anxiety. Relief from dysthymia had continued for about 2 years with KUT treatment.

- Case 3: A 61-year-old woman developed a feeling of heavy head and sleeplessness. She was receiving atorvastatin for hyperlipidemia and had also received a sleep-aid drug from a local hospital, but her symptoms persisted, followed by the development of depressive symptoms and malaise. She requested Kampo medicine 2.5 years after her initial visit. She was diagnosed as having dysthymic disorder based on DSM-IV. Kousosanryo therapy for 8 weeks failed to improve dysthymia. Her symptoms were relieved by 80% after 4 months of KUT administration, and thereafter, she was able to concentrate on work (as a pharmacist) and housekeeping. Improvement of dysthymia had continued for 18 months with KUT treatment.
- Case 4: A 53-year-old woman (menopause at 51 years old) requested Kampo medicine for dysthymic disorder with sleeplessness, malaise, and nervousness, without menopausal vasomotor symptoms, which had persisted for about 5 years. She was a housewife and could barely perform housework. She had not been taking antidepressant therapy, although she was taking hypotensive drugs for hypertension. Depressive symptoms were relieved after 4 months of KUT treatment and the improvement continued for 6 months. However, sleeplessness, easy fatigability and appetite loss reappeared. Therefore, KUT was replaced with another Kampo formula (Kamikihito) and she showed improvement by 50%.
- Additional patients: Two additional patients with depressive symptoms for less than 2 years (and did not fulfill the criteria for dysthymia) were also successfully treated with KUT.

***Human research to suggest benefits to patients with dementia***:

In an open-label randomized controlled trial of 84 Alzheimer's patients, 18 patients were administered KUT for 36 weeks while the remaining 66 patients were untreated controls (Suzuki et al., 2001). After 3 weeks, cognitive function measured by MMSE increased 1.8 points in the KUT group and then declined thereafter, while the control group showed consistent decline from the start of the study. After 36 weeks (and at every time point after 3 weeks), the KUT group had significantly better MMSE scores compared to the untreated control group. Because the study was not placebo-controlled, placebo effects cannot be ruled out.

In an open-label controlled trial of 52 Alzheimer's patients, treatment with KUT (31.5 g daily, dissolved in water and taken half of the amount twice daily) for 12 months significantly slowed the rate of cognitive decline compared to untreated control patients (p=0.04)(Arai et al., 2000). After 12 months, the KUT group (n=20) had an MMSE decline of 1.4 points while the untreated control group (n=32) had a decline of 4.1 points. The efficacy of KUT was most prominent at 3 months. At 1 and 3 months, the KUT group showed an improvement in MMSE (p=0.001 compared to control at 3 months), then declined thereafter.

The control group showed consistent decline during the duration of the study. There were no significant effects of KUT for CSF measures of tau and Aβ42. KUT treatment increased brain metabolism across the cerebral cortex, measured by FDG-PET, compared to baseline. Because the study was not placebo-controlled, placebo effects cannot be ruled out.

In an observer-blind randomized controlled clinical trial of 38 mild to moderate Alzheimer's disease patients, the combination of KUT and donepezil (3 mg daily for 2 weeks, then 5 mg daily thereafter) for 12 weeks was compared with donepezil alone (Maruyama et al., 2006). Relative to baseline, post-treatment cognitive (MMSE) scores significantly improved only in the KUT + donepezil combination group (baseline, 18.9±4.9; post-treatment, 21.6±4.2 points; p=0.001; 95% confidence interval [CI], -4.17 to -1.28) but not in the donepezil monotherapy group (baseline, 19.6±4.1; post-treatment, 20.4±4.5). Another cognitive score, the ADAS-cog, also improved significantly in the KUT + donepezil combination group (baseline, 21.0±7.6; post-treatment, 16.8±7.1; p<0.001; 95% CI, 2.54 to 5.80) but no improvement was seen in the donepezil monotherapy group (baseline, 19.5±6.8; post-treatment, 18.2±7.0). Cerebral blood flow in frontal regions significantly increased in the KUT + donepezil combination group compared to baseline (p<0.05 in the Brodmann's area 9 and 8). No statistically significant differences in cognitive scores or cerebral blood flow were reported between the KUT + donepezil versus donepezil monotherapy groups post-treatment.

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

In aged rats (2-year-old rats), KUT treatment (taken orally in drinking water) significantly improved memory deficits measured by the passive avoidance test and restored ChAT activity in the frontoparietal cortex (Yabe et al., 1996). Passive avoidance performance in KUT-treated aged rats was comparable to that of young adult rats (3-month-old). Also in aged rats, KUT treatment increased ChAT mRNA levels by ~1.8-fold in the basal forebrain and increased nerve growth factor (NGF) mRNA levels by 2.8-fold in the frontoparietal cortex, measured by RT-PCR.

In 18-month-old aged mice, KUT treatment for 3 months significantly increased acetylcholine levels in the cortex, striatum, hippocampus, and the whole brain, compared to control mice (Wang et al., 2000). Immunohistochemistry studies showed that the densities of ChAT-immunoreactive cells in the medial septum, vertical limbs of the diagonal band of Broca, and the nucleus basalis Meynert were significantly increased with KUT treatment.

In a rat model of cognitive dysfunction (induced by ibotenic acid injection into the basal forebrain), treatment with KUT (started on the same day as the ibotenic acid injection; taken orally in drinking water) attenuated memory deficits (measured by the passive avoidance task) and restored ChAT activity in the cerebral cortex (Yabe et al., 1995). Also in the same rat model, treatment with Polygalae Radix extract (500 mg/kg, orally), a component of KUT, also restored ChAT activity in the frontal cortex (Yabe et al., 1997). Treatment with sinapinic acid (100 mg/kg, orally), a phenolic compound found in Polygalae Radix, also increased ChAT activity in the frontal cortex of basal forebrain-lesioned rats.

In a mouse model of memory impairment induced by thiamine deficiency, KUT treatment protected against memory impairment (measured by passive avoidance task) when KUT was administered concurrently with the thiamine-deficient diet (Nakagawasai et al., 2024). KUT treatment also protected against the thiamine deficiency-induced decline in hippocampal ChAT. In the same mouse model, KUT treatment also prevented depression-like behavior (measured by the forced swim test) induced by thiamine deficiency. This occurred concurrently with protection against a decrease in tyrosine hydroxylase, the rate-limiting enzyme for synthesis of catecholamines (dopamine, norepinephrine, and epinephrine)(Nakagawasai et al., 2007).

In a mouse model of chronic mild stress (forced swimming, cage tilt, dirty cage, vibrating cage), KUT treatment (1 g/kg, orally) for 11 days significantly ameliorated depression-like behavior, measured by the forced swim test, and restored hippocampal neurogenesis, measured by BrdU (Yabe, 2016). In another mouse model of stress (induced by chronic corticosterone injection), concurrent treatment with KUT also ameliorated depression-like behavior and restored hippocampal neurogenesis (increased BrdU). Also in corticosterone-injected mice, concurrent administration of one of KUT's ingredients, Polygalae radix (orally), for 14 days significantly reduced depression-like behavior and increased the expression of GDNF mRNA and the number of hippocampal dendritic spines. No effects of KUT or Polygalae radix extract were seen on mRNA levels of FGF2, VEGF, BDNF, NGF, IGF1, or NT-3.

In a mouse model of anxiety/depression (isolation-reared), KUT treatment (1 g/kg, orally) reduced anxiety/depression-like behavior, measured by the forced swim test and behavioral response to an unfamiliar mouse (Araki et al., 2019). When KUT was administered orally, extracellular serotonin levels significantly increased in the prefrontal cortex and peaked at 40 minutes post-administration. In the same mouse model, KUT treatment (1 g/kg, orally) reversed anxiety/depression-like behavior, measured by the forced swim test and social encounter test, in a manner similar to the SSRI fluoxetine (30 mg/kg)(Hiraki et al., 2019). *In vivo* microdialysis studies showed that KUT transiently increased the levels of extracellular serotonin levels in the prefrontal cortex without affecting dopamine or norepinephrine

levels. KUT with the Bambusae Caulis component removed failed to improve depression-like behavior or increase prefrontalserotonin levels. However, Bambusae Caulis alone did not produce anti-depressant-like effects or increase prefrontal serotonin levels, suggesting that Bambusae Caulis and other herbs may act together to produce these effects.

In rat embryo basal forebrain cell culture, KUT administration (200 µg/ml) for 3 days significantly increased ChAT activity (Yabe and Yamada, 1997). In rat embryo astroglial culture, KUT administration (12.5-400 µg/ml) for over 24 hours significantly increased the amount of NGF secreted by quiescent astrocytes in a dose-dependent manner. However, KUT did not affect the proliferation of astroglial cells. KUT administration also increased levels of ChAT mRNA in basal forebrain cells and NGF mRNA in cerebral cortex cells.

In basal forebrain cells, administration of Polygalae Radix extract increased ChAT activity and ChAT mRNA levels (Yabe et al., 1997).

In astroglial cell culture, administration of KUT led to immediate induction of intracellular cAMP and expression of c-fos mRNA (Yabe and Yamada, 1997). This was followed by induction of NGF mRNA. Addition of KUT to astroglial culture also increased levels of BDNF mRNA at 1, 2, and 6 hours.

In astroglial cells, Polygalae Radix extract induced NGF secretion (Yabe et al., 1997).

Together, Polygalae Radix appears to be a critical component of KUT in enhancing ChAT activity and NGF secretion.

***APOE4 interactions***:

In an open-label controlled trial of 52 Alzheimer's patients, the effects of KUT treatment (31.5 g daily, dissolved in water and taken half of the amount twice daily) for 12 months did not vary significantly based on APOE status (Arai et al., 2000). There was a 2.2 point decline in MMSE in APOE3/3 subjects (n=6), 1.2 point decline in APOE4/2 and 4/3 subjects (n=8), and 0.1 point decline in E4 homozygotes (n=7).

**Aging and related health concerns:** Studies in mouse models of aging and memory impairment reported higher survival rates with KUT treatment. No studies in humans have evaluated whether KUT increases lifespan or decreases age-related diseases.

*Types of evidence:*

- A few laboratory studies

***Lifespan***: POTENTIALLY INCREASED IN MICE

No studies have evaluated whether KUT increases lifespan/healthspan or decreases mortality in humans.

In 18-month-old aged mice, KUT treatment for 3 months resulted in 87.5% (35/40) of the mice surviving during the study, while only 63% (17/27) of untreated mice survived in the same time-frame; survival rate was significantly higher in the KUT-treated mice (p=0.03)(Wang et al., 2000).

In a mouse model of memory impairment induced by thiamine deficiency, 30-day survival was 33.3%, but when treated with KUT, they had a 30-day survival rate of 90% (Nakagawasai et al., 2024).

**Safety:** While KUT has a long history of use in Japan, there have been no large, randomized placebo-controlled trials testing the long-term safety of KUT. Rarely, Glycyrrhiza radix can lower K+ levels and increase blood pressure and edema.

*Types of evidence:*

- 2 clinical trials
- 1 case study
- Several laboratory studies

In an open-label controlled trial of 52 Alzheimer's patients, treatment with KUT (31.5 g daily, dissolved in water and taken half of the amount twice daily) for 12 months did not result in nausea, vomiting, or diarrhea (Arai et al., 2000).

In an observer-blind randomized controlled clinical trial of 38 mild to moderate Alzheimer's disease patients, the combination of KUT and donepezil (3 mg daily for 2 weeks, then 5 mg daily thereafter) for

12 weeks did not result in any cholinergic adverse events such as diarrhea, but 2 patients in the donepezil monotherapy group had intractable diarrhea (Maruyama et al., 2006).

In case studies of 4 patients with dysthymic disorder and general malaise who were successfully treated with KUT, there were no adverse reactions attributable to KUT during the follow-up periods lasting up to 3 years (Kogure et al., 2010).

Although rarely reported, Glycyrrhiza radix, a component of KUT, can lower potassium levels (through accelerated excretion via the renal tubules), leading to increased blood pressure from fluid retention and myopathy (due to low potassium levels).

***Drug interactions***:

Herb-drug interactions with KUT have not been studied extensively. KUT appears to be well-tolerated in combination with donepezil (Maruyama et al., 2006).

**Sources and dosing:**

KUT is available with prescription in Japan. KUT is a type of Kampo medicine that consists of 13 types of dried medicinal herbs. The following herbs are mixed with 600 ml of water and boiled down to 300 ml, and the aqueous extract is filtered through a sieve: Pinelliae tuber (5.0 g), Hoelen (4.0 g), Aurantii Nobilis Pericarpium (3.0 g), Banbusae Caulis (3.0 g), Polygalae Radix (2.0 g), Glycyrrhizae Radix (2.0 g), Scrophulariae Radix (2.0 g), Aurantii Fructus Immaturus (2.0 g), Zizyphi Semen (2.0 g), Rehmanniae Radix (2.0 g), Zizyphi Fructus (2.0 g), Ginseng Radix (2.0 g), and Zingiberis Rhizoma (1.0 g). Typical commercial products come in dried powder form (2.0 g per serving) and is dissolved in water and taken before meals, typically twice or three times a day, orally (Kracie leaflet).

**Research underway:**

There are no ongoing clinical trials testing kamiuntanto for cognitive decline or dementia.

**Search terms:**

Pubmed, Google: kamiuntanto, 加味温胆湯

Websites visited for kamiuntanto:

- Clinicaltrials.gov (0)
- NIH RePORTER (0)
- DrugAge (0)
- Drugs.com (0)
- WebMD.com (0)
- DrugBank.ca (0)