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.

PTI-00703

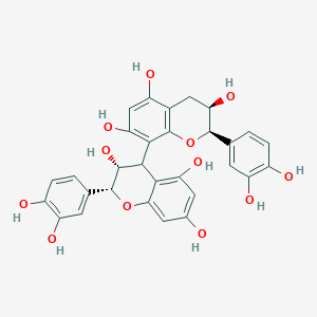
Evidence Summary

PTI-00703 prevents the formation of, and dissolves existing, plaques and tangles in preclinical models, but no data on clinical efficacy or safety exist for humans.

Neuroprotective Benefit: Preclinical studies suggest that PTI-00703 or its components inhibit formation of plaques and tangles, reduce astrocytosis and microgliosis, and improve memory (in mice), but no studies have confirmed these effects in humans.

Aging and related health concerns: No studies have investigated PTI-00703 for age-related peripheral conditions. Cat's claw has been used in alternative medicine for improving symptoms of arthritis.

Safety: No toxicology data are available for PTI-00703 and no clinical trials have tested this formulation. Reported adverse events with cat's claw extract include gastritis, headache, vomiting, and dizziness, but the rates appear comparable to placebo.

Availability: OTC	**Dose:** Not established; PTI-00703 has not been tested in human clinical trials.	**Chemical formula:** e.g., $C_{30}H_{26}O_{12}$ for proanthocyanidin B2
Half life: Unknown.	**BBB:** Major ingredients of PTI-00703 are bbb-penetrant based on rodent studies.	**MW:** 578.52 for proanthocyanidin B2
Clinical trials: none with PTI-00703	**Observational studies:** none with PTI-00703	 Source: PubChem

What is it? Cat's claw is a medicinal plant originating from the Amazon River basin and has been used for the treatment of chronic inflammation such as arthritis. PTI-00703 is an extract from a cat's claw species called *Uncaria tomentosa* (a Peruvian source) and was identified as having Aβ- and tau tangle-reducing activities based on plaque and tangle screening tools (Snow et al., 2019). An epicatechin-dimer with the structure of epicatechin-4β-8-epicatechin (also known as proanthocyanidin B2) is the major component of PTI-00703 that has plaque- and tangle-dissolving and inhibitory activity. Other polyphenols in PTI-00703 that demonstrated plaque-reducing activity included proanthocyanidin B4, proanthocyanidin C1, an epicatechin trimer, and an epicatechin tetramer. PTI-00703's 11–13 major polyphenolic components are referred to as PTI-777.

Neuroprotective Benefit: Preclinical studies suggest that PTI-00703 or its components inhibit formation of plaques and tangles, reduce astrocytosis and microgliosis, and improve memory (in mice), but no studies have confirmed these effects in humans.

Types of evidence:

- 2 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:
None available.

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

In vitro studies with PTI-00703: In *in vitro* studies, PTI-00703 cat's claw significantly and dose-dependently inhibited Aβ40 fibril formation, dissolved pre-formed Aβ42 fibrils within minutes, inhibited tau protein from forming paired helical filaments/tau fibrils, and dissolved tau protein tangles (Snow et al., 2019).

In an earlier x-ray diffraction study where 20 different compounds (e.g., curcumin, melatonin, nicotine, tannic acid, etc.) were screened for inhibitors of Aβ fibril formation, PTI-00703 cat's claw was the most effective inhibitor/disaggregator of pre-formed Aβ fibrils (Kirschner et al., 2008). Using the volume of the β-crystallites as a measure of inhibition, the effectiveness was in the order of: PTI-00703 > tannic acid > quinine > tetracycline ~ tetrachlorosalicylanilide ~ teracaine ~ hexachlorophene > sulfadiazine > melatonin ~ butylated hydroxytoluene > morin ~ Aβ(11-25) control > phenolphthaleine > chloramphenicol > curcumin > ethyl 3-aminobenzoate methanesulfonate.

PTI-00703 cat's claw abolished the H-bonding reflection indicative of the β-sheet secondary structure present in Aβ fibrils. The most effective and potent plaque and/or tangle inhibitors and disrupters consisted of aromatic polyhydroxylated compounds containing two or more adjacent hydroxyl groups (i.e., catechol groups), such as found in epicatechin, catechin, ECG, and ECGC. In contrast to chlorogenic acid and epicatechin which contain one catechol group, the most effective major component identified in PTI-00703 cat's claw was a dimeric epicatechin, proanthocyanidin B2. The position and spacing of the two catechol groups is apparently important for the inhibition and dissolution of plaques and tangles. A replacement of catechol groups on the aromatic rings with methyl groups led to the disappearance of these activities (Snow et al., 2019).

Rodent studies with PTI-777: The PTI-777 fraction of PTI-00703 included polyphenolic compounds including chlorigenic acid, epicatechin, proanthocyanidin B2, proanthocyanidin B4, proanthocyanidin C1, and epiafzelechin-4β-8-epicatechin (Snow et al., 2019).

In an 8-month old transgenic mouse model of Alzheimer's disease (TASD-41 APP double transgenic mice), treatment with PTI-777 for 14 days significantly reduced Aβ load by 59% and plaque number by 78% in the hippocampus and cortex (Snow et al., 2019). In male and female rats, PTI-777 crossed the blood-brain-barrier and entered the brain parenchyma within 2 minutes of being injected intravenously. About 18,000 dpm/g tissue of 3H-PTI-777 was found in the brain within 5 minutes of a single intravenous administration. By 1 hour, levels decreased to ~10,100 dpm/g and at 24 hours, the brain tissue contained about ~7,000 dpm/g of 3H-PTI-777 (~41% of the peak brain level).

When PTI-777 (25 mg/kg, i.p.) was administered for 30 days in 6-month old TASD-41 APP transgenic mice, there was a 33.2% reduction in Aβ load and a 56.6% reduction in amyloid plaque number (per mm^2)(Snow et al., 2019).

Rodent studies with proanthocyanidin B2: Of the compounds present in PTI-00703, the one most effective at disassembly/disaggregation of Aβ42 fibrils was proanthocyanidin B2 (Snow et al., 2019).

When proanthocyanidin B2 (50 mg/kg/day, i.p.) was administered for 90 days in 4-month old TASD-41 APP transgenic mice, there were significant reductions in the levels of soluble and insoluble Aβ42 and Aβ40 in the cortex (Snow et al., 2019). Levels of insoluble Aβ42 and Aβ40 were decreased by 18.5% and 23.9%, respectively. Levels of soluble Aβ42 and Aβ40 were decreased by 70.4% and 58.9%, respectively. In these mice, there was a 74.9% reduction in plaque number compared to saline-treated APP mice. In 6-month old TASD-41 APP transgenic mice that were treated with proanthocyanidin B2 for 90 days, a similar reduction in brain amyloid load and plaque number was found. In these older mice, proanthocyanidin B2 treatment resulted in a 58.2% reduction in Aβ protein load and a 51.9% reduction in plaque number compared to saline-treated mice.

Proanthocyanidin B2 treatment also caused a significant reduction in astrocytosis and microgliosis, as measured by a 69.0% decrease in GFAP-immunostaining and an 80.3% reduction in MHC-II immunostaining in brain sections.

Proanthocyanidin B2 treatment (50 mg/kg/day, i.p.) also improved hippocampus-dependent memory (measured by the Morris water maze) in TASD-41 APP mice such that their performance approached that observed in non-transgenic mice (Snow et al., 2019).

Caveats: While these preclinical studies appear promising, numerous drugs targeting Aβ have been unsuccessful in altering the progression of Alzheimer's in large phase 3 clinical trials (Shih et al., 2018).

It is also worth noting that there are many food sources of proanthocyanidins, including red grapes, red wine, bilberries, cranberries, blueberries, cocoa beans, ginkgo biloba, and others. So far clinical trials testing ginkgo biloba have not produced clinically meaningful positive results in dementia patients (Birks et al., 2009). Clinical studies with cocoa have also produced small benefits with no evidence yet of whether it can protect against dementia (CognitiveVitality Cocoa rating). A phase 2 study examining the effects of grape seed extract in Alzheimer's is ongoing and scheduled to be completed in September 2020 (NCT02033941).

APOE4 interactions: Unknown.

Aging and related health concerns: No studies have investigated PTI-00703 for age-related peripheral conditions. Cat's claw has been used in alternative medicine for improving symptoms of arthritis.

Types of evidence:

- None on PTI-00703
- A few clinical trials with cat's claw extract

No studies have investigated PTI-00703 for age-related conditions beyond what is described above for neuroprotection. However, some studies have examined cat's claw.

Arthritis: UNKNOWN. Although no data exist for PTI-00703, cat's claw has been used in alternative medicine for improving symptoms of osteoarthritis and rheumatoid arthritis (Drugs.com). In a double-blind randomized controlled trial of 40 patients with rheumatoid arthritis who were taking sulfasalazine or hydroxychloroquine, an adjunct treatment with cat's claw (*Uncaria tomentosa*; same species as the origin of PTI-00703) for 24 weeks resulted in a reduction in the number of painful joints compared to placebo (by 53.2% vs 24.1%; p = 0.044)(Mur E et al., 2002). Patients originally receiving the placebo for 24 weeks received the cat's claw extract during the open-label extension of 28 weeks and these patients experienced a reduction in the number of painful (p = 0.003) and swollen joints (p = 0.007) and the Ritchie Index (p = 0.004) compared to the values after 24 weeks of placebo.

In a double-blind randomized controlled trial of 45 patients with osteoarthritis, a freeze-dried form of a different species of cat's claw (*Uncaria guianensis*, 1 capsule of 100 mg/day; different from *Uncaria tomentosa* where PTI-00703 comes from) for 4 weeks significantly reduced pain associated with

activity, with benefits occurring within the first week of therapy (Piscoya et al., 2001). However, knee pain at rest or at night, and knee circumference were not significantly reduced by cat's claw treatment. *In vitro* tests indicated that both species of cat's claw (*Uncaria guianensis* and *Uncaria tomentosa*) quenched the free radical DPPH equally well (EC50, 13.6-21.7 µg/ml) and both inhibited TNF-α production. Cat's claw (10 µg/ml) had no effect on basal PGE2 production, but reduced LPS-induced PGE2 release, though this effect was observed at higher concentrations than that required for TNF-α inhibition. The anti-inflammatory properties of cat's claw may be attributed to its ability to inhibit TNF-α, and to a lesser extent, PGE2 production.

Based on a review on the mechanisms of action of cat's claw in alleviating osteoarthritis, cat's claw has been found to inhibit inflammation (LPS)-induced iNOS gene expression, nitrate formation, cell death, PGE2 production, and the activation of NF-κB and TNF-α (Hardin, 2007). Cytokines such as IL-1, TNF-α, and nitric oxide (NO) are triggered by the chondrocytes, synoviocytes, fibroblasts and inflammatory cells. IL-1 is the catalyst for the production of destructive proteases and inhibition of articular cartilage proteoglycan synthesis. Two other interleukins, IL-17 and IL-18, have also been found in osteoarthritis joints to cause destructive proteases and induction of NO synthesis. NO is a mediator of cartilage pathology stimulated by IL-1, TNFα, and IL-17. TNF-α is a driving force of IL-1 synthesis and regulation of cytokine production. Upregulation of the TNF-α p55 receptor is associated with loss of articular cartilage. IL-1 and TNF-α promote the nuclear translocation of NF-κB, which in turn regulates genes involved in inflammation. NF-κB regulates the production of matrix metalloproteases by chondrocytes. Both species of cat's claw (*Uncaria tomentosa* and *Uncaria guianensis*) were found to suppress the redox-sensitive regulation of gene expression, act as a free radical scavenger, suppress TNF-α and apoptosis, and protect against potent oxidants such as peroxynitrite.

Cancer: UNKNOWN. No clinical trials have examined whether PTI-00703 or cat's claw more generally can prevent or treat cancers. A prospective phase 2 open-label clinical trial in 51 patients with advanced solid tumor reported that cat's claw treatment (dry extract of *Uncaria tomentosa*, 100 mg dose 3 times per day) improved the patients' overall quality of life (p=0.0411) and social functioning (p=0.0341; as assessed by the EORTC QLQ C-30), and reduced fatigue (p=0.0496; assessed by the Chalder Fatigue Questionnaire)(de Paula et al., 2015). However, none of the biochemical or inflammatory parameters assessed (IL-1 and -6, CRP, TNF-α, erythrocyte sedimentation rate, and α-1-acid glycoprotein) changed significantly and no tumor response was detected according to the Response Evaluation Criteria In Solid Tumors. Details of this study could not be evaluated as the full text was inaccessible.

A few other clinical studies have tested cat's claw's benefits in reducing side effects from chemotherapy (Santos Araujo Mdo et al., 2012; Farias et al., 2012).

Safety: No toxicology data are available for PTI-00703 and no clinical trials have tested this formulation. Reported adverse events with cat's claw extract include gastritis, headache, vomiting, and dizziness, but the rates appear comparable to placebo.

Types of evidence:

- 1 rodent study with PTI-00703
- A few clinical trials with cat's claw extract

Preclinical: UNKNOWN. There has only been one study in rodents that tested PTI-00703 (Snow et al., 2019). No toxicology studies have been carried out, though *in vivo* studies following injection of PTI-777 (11–13 major polyphenolic components of PTI-00703) or peripheral administration of proanthocyanidin B2 (the major plaque/tangle-dissolving component of PTI-00703) did not result in neuronal loss or apparent cellular toxicity in the brain following up to 6 months of treatment. No information is currently available on acute toxicity, subacute toxicity, subchronic/chronic toxicity, immunotoxicity, reproductive toxicity, genotoxicity/mutagenicity, carcinogenicity, or other laboratory animal toxicology measures. Although PTI-00703 produced immediate results in dissolving plaques and tangles, it is unknown what other harmful or beneficial proteins it may dissolve.

Clinical: UNKNOWN FOR PTI-00703; A FEW ADVERSE EFFECTS WITH CAT'S CLAW. In a double-blind randomized controlled trial of 40 patients with rheumatoid arthritis who were taking sulfasalazine or hydroxychloroquine, an adjunct treatment with cat's claw (*Uncaria tomentosa*; same species as the origin of PTI-00703) for 24 weeks resulted in adverse events in 12 patients in each group (Mur E et al., 2002). One patient taking the cat's claw extract withdrew from the study due to gastritis and one patient from the placebo group due to diarrhea. In the open-label extension phase, 7 other side effects were observed, though none were clearly attributed to the treatment. No major side effects were seen in the active or the placebo group.

In a double-blind randomized controlled trial of 45 patients with osteoarthritis, treatment with a freeze-dried form of a different species of cat's claw (*Uncaria guianensis*, 1 capsule of 100 mg/day; different from *Uncaria tomentosa* where PTI-00703 comes from) for 4 weeks had no deleterious effects on blood or liver function or other significant side-effects compared to placebo (Piscoya et al., 2001). There were also no differences in the incidence and form of side effects reported by the cat's claw

versus placebo groups. At week 1, 1 patient in the cat's claw group presented with vomiting and 1 with dizziness. At week 2, the cat's claw group had 5 patients reporting headache, and at week 4, 3 patients in the cat's claw group and 1 patient in the placebo group presented with headache; 1 patient in the placebo group reported dizziness and 1 reported ringing in the ears.

Drug interactions: Drug interactions with PTI-00703 are not well-studied. When taking cat's claw supplements, avoid taking other herbal supplements such as casein protein, coenzyme Q10, fish oil, L-arginine, lyceum, or stinging nettle as the combination may cause your blood pressure to get too low (Drugs.com). Cat's claw should not be taken when pregnant as it could harm the unborn baby. It is also not known whether cat's claw passes into breast milk, so you should not breast-feed while taking cat's claw.

Sources and dosing: PTI-00703 comes from a specific commercial manufacturer where the extract is isolated from Peruvian cat's claw (*Uncaria tomentosa*). There are 34 species of cat's claw (other than *Uncaria tomentosa*) and each species contains different amounts and types of compounds based on where it is harvested and the extraction process (Gonzales and Valerio, 2006).

PTI-00703 cat's claw represents a 70% ethanol/water extract of *Uncaria tomentosa* bark powder that is filtered to remove high molecular weight material and concentrated by spray drying (Snow et al., 2019). The authors of this preclinical study have tested ~10 different sources of *Uncaria tomentosa* for specific Aβ42 fibril- and plaque-dissolving activity from Europe, Brazil, Peru, and the US, and identified one Peruvian source that produces the most robust activity (Snow et al., unpublished data).

A new product called Percepta® is being sold in the US and contains PTI-00703® cat's claw in addition to a specific oolong tea extract called MemorTea® (PerceptaBrain.com). Percepta® co-founders are Alan Snow, PhD, first author of the 2019 preclinical study, and Rudy Tanzi, PhD, professor of neurology at Harvard University.

Research underway: No clinical trials are currently underway to test the efficacy of PTI-00703.

Search terms:
Pubmed, Google:

- PTI-00703, cat's claw, proanthocyanidin

Websites visited for PTI-00703, cat's claw:

- Clinicaltrials.gov
- Examine.com (0)
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com (cat's claw)
- WebMD.com (cat's claw)
- PubChem (0)
- DrugBank.ca (0)
- Labdoor.com (0)
- Cafepharma (0)
- Pharmapro.com (0)