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.

Angiotensin 1-7

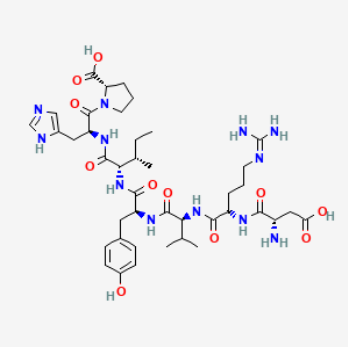
Evidence Summary

Numerous laboratory studies have shown neuroprotective, vasodilative, anti-inflammatory, and anti-oxidative effects of Ang1-7. Because of its short half-life, modified compounds hold greater promise.

Neuroprotective Benefit: Ang1-7 levels are lower in Alzheimer's patients. Numerous laboratory studies have shown pro-cognitive and neuroprotective effects of Ang1-7. Because of the short half-life, analogs and modified compounds hold greater promise.

Aging and related health concerns: Clinical evidence is limited, but evidence from laboratory studies suggest potential benefits for cancer, cardiovascular diseases, type 2 diabetes, and ocular diseases.

Safety: A few small clinical trials have shown that short-term treatment with Ang1-7 is well-tolerated, though long-term safety is not established.

Availability: TXA-127 is a pharmaceutically formulated Ang1-7; Ang1-7 analogs are also under development	**Dose**: Dose has not been established for any indication. A pilot study in COVID-19 patients tested a dose of 0.5 mg/kg, daily, intravenously for 10 days.	**Chemical formula:** $C_{41}H_{62}N_{12}O_{11}$ **MW**: 899.0  Source: PubChem
Half-life: plasma half-life is around 30 minutes	**BBB**: not penetrant; some Ang1-7 analogs can cross the BBB	
Clinical trials: Several small clinical trials have tested Ang1-7: one in 34 patients with cancer, one in 20 breast cancer patients, and one in 22 COVID-19 patients.	**Observational studies**: none	

What is it?

Angiotensin 1-7 (Ang1-7) is a heptapeptide of the renin-angiotensin system (RAS), which plays a role in cardiovascular and renal systems. RAS has two main axes. The classical axis is composed of the angiotensin-converting enzyme (ACE), angiotensin II (AngII), and angiotensin type 1 receptor (AT1R), and this axis plays a role in vasoconstriction, inflammation, oxidative damage, endothelial dysfunction, fibrosis, atherosclerosis, and cell death (Santos et al., 2013; Hernandez et al., 2021; Annoni et al., 2022). The opposing axis is composed of ACE2, Ang1-7, and the Mas receptor; and this axis counter-regulates the classical axis by promoting vasodilation, anti-inflammation, anti-oxidation, and decreasing proliferation, hypertrophy, fibrosis, and thrombosis. Ang1-7 is formed by the transformation of AngII by ACE2, or through hydrolysis of AngI to Ang1-9, then conversion of Ang1-9 to Ang1-7 by ACE. The Ang1-7/Mas pathway promotes neuroprotection through multiple ways: increased cerebral flow (increased eNOS and NO), decreased reactive oxygen species (decreased iNOS and NADPH), increased neurogenesis (increased BDNF, gCSF), decreased inflammation (decreased TNF-α and NFkB), and increased angiogenesis (VEGF) (Hernandez et al., 2021).

Because Ang1-7 is a peptide, it is susceptible to degradation and has a short half-life of around 30 minutes (Annoni et al., 2022). Stabilized forms of Ang1-7 are currently under development.

Neuroprotective Benefit: Ang1-7 levels are lower in Alzheimer's patients. Numerous laboratory studies have shown pro-cognitive and neuroprotective effects of Ang1-7. Because of the short half-life, analogs and modified compounds hold greater promise.

Types of evidence:

- 2 observational studies examining plasma levels of Ang1-7 in Alzheimer's patients
- 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:

No clinical trials have tested Ang1-7 to treat dementia. There have been two studies examining Ang1-7 levels in relation to Alzheimer's disease suggesting that the alternative RAS axis is downregulated in Alzheimer's disease. In a pilot biomarker cross-sectional, case-control study of 14 Alzheimer's patients and 14 age-matched controls, plasma levels of Ang1-7 were significantly lower in Alzheimer's patients than in controls [median (25^{th}-75^{th} percentiles): 101.5 (62.43–126.4) in Alzheimer's patients; 209.3 (72–419.1) in controls](Ribeiro et al., 2021). There was no significant difference in circulating levels of AngII. In Alzheimer's patients, Ang1-7 values positively correlated with white matter hypointensity volumes, but not with cortical volumes; this correlation was not present in age-matched controls. In another biomarker study of 110 Alzheimer's patients and 128 age/sex-matched controls, plasma levels of Ang1-7 was significantly lower in Alzheimer's patients (15.63±4.35 pg/mL) compared to controls (19.58±3.22 pg/mL)(Jiang et al., 2016). Ang1-7 levels positively correlated with cognitive functions. A receiver-operating characteristic analysis showed that plasma Ang1-7 levels can distinguish Alzheimer's patients from controls with the sensitivity and specificity of 69.1% and 74.2%, respectively, when using the cut-off value of 18.2 pg/ml.

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

The ACE2/Ang1-7/Mas axis exerts effects that oppose the classical RAS axis involving ACE/AngII/AT1R, leading to vasodilative, anti-inflammatory, and anti-oxidative effects (Annoni et al., 2022).

Ang1-7 stimulates numerous pathways that may result in neuroprotection, including increased endothelial nitric oxide synthase (eNOS), the neurotrophic factor BDNF, and the vascular endothelial growth factor (VEGF), and decreased reactive oxygen species and pro-inflammatory cytokines (reviewed in Hernandez et al., 2021). Ang1-7 can also act directly on microglial cells to reduce the release of pro-inflammatory cytokines (IL-1β and TNF-α), while increasing the anti-inflammatory cytokine IL-10 (Liu et al., 2015). There have been numerous preclinical studies that have shown anti-inflammatory and neuroprotective effects of Ang1-7 in rodent models of cognitive impairment, Alzheimer's disease, Parkinson's disease, stroke, brain injury, and heart failure (Annoni et al., 2022).

Alzheimer's disease: Ang1-7 has been studied in several rodent models of Alzheimer's disease and appear to show consistent benefits. No studies have tested Ang1-7 or its analogs in human patients of Alzheimer's disease.

In a mouse model of Alzheimer's disease (5xFAD mice), intracerebroventricular infusion of Ang1-7 (500 ng/kg/hour, Peptide Institute Inc, Japan) for 4 weeks significantly ameliorated cognitive impairment (measured by the Morris water maze) while increasing cerebral blood flow and cerebrovascular reactivity (Uekawa et al., 2016). This treatment did not alter levels of hippocampal or cortical amyloid plaques, soluble Aβ42, or soluble Aβ oligomers. In this same mouse model, treatment with Ang1-7 (400 ng/kg/min subcutaneously via an osmotic minipump) for 4 weeks counteracted the AngII-induced cognitive dysfunction and skeletal muscle atrophy without influencing blood pressure (Cao et al., 2019).

In rats receiving intracerebroventricular administration of Aβ42, Ang1-7 treatment attenuated the cognitive impairment, as measured by the Morris water maze and spontaneous alteration behavior in the Y-maze test (Varshney and Garabadu, 2021). Ang1-7 treatment attenuated the Aβ-induced cholinergic dysfunction (measured by levels of ACh and activities of ChAT and AChE) and the increase in Aβ in the hippocampus, prefrontal cortex and amygdala, while alleviating the changes in mitochondrial function, integrity, and bioenergetics.

In the APP/PS1 mice, treatment with a non-peptide analog of Ang1-7, AVE0991 (10 mg/kg, i.p., MedChemExpress LLC, NJ, USA) for 30 days rescued cognitive impairment and alleviated neuronal and synaptic damage (Duan et al., 2021). AVE0991 treatment suppressed astrocytic NLRP3 inflammasome-mediated neuroinflammation (measured by significantly lower protein levels of IL-1β, IL-6 and TNF-α) via the SNHG14/miR-223-3p/NLRP3 pathway, but did not affect levels of Aβ42. AVE0991 crosses the blood-brain barrier (Xue et al., 2021).

In a model of sporadic Alzheimer's disease (SAMP8 mice), Ang1-7 levels in the hippocampus and cerebral cortex were significantly reduced during disease progression, and an inverse correlation was found between Ang1-7 levels and tau hyperphosphorylation (Jiang et al., 2016). This inverse correlation was confirmed in a different Alzheimer's disease model (P301S mice) of pure tauopathy.

Vascular cognitive impairment and dementia (VCID): In a mouse model of VCID (congestive heart failure induced by ligation of the left coronary artery to instigate a myocardial infarction), treatment with Ang1-7 (50 µg/kg/hr, subcutaneously with an osmotic pump) for 4 weeks significantly restored cognitive functions (novel object recognition task) such that they performed similar to sham-operated mice, and significantly better than saline-treated VCID mice (Hay et al., 2017). Ang1-7 treatment also improved spatial memory as measured by the Morris water maze test. Ang1-7 treatment did not have any effects on cardiac function (e.g., ejection fraction).

In the same mouse model of VCID, treatment with a glycosylated Ang1-7 MasR agonist peptide, PNA5 (1 mg/kg, s.c.), for 21 days showed better brain penetration than Ang1-7 and exhibited cognitively protective effects that lasted up to 10 days beyond the peptide's half-life (Hay et al., 2019). PNA5 (Ang-1-6-O-Ser-Glc-NH2; molecular weight of 1278) was designed to improve bioavailability, stability, and brain penetrance of Ang1-7. PNA5 treatment reversed impairments in object recognition and spatial memory while increasing the anti-inflammatory cytokine IL-10 and inhibiting inflammation biomarkers (TNF-α, IL-7, and granulocyte cell-stimulating factor). PNA5 activation of the MasR showed a dose-dependent inhibition of reactive oxygen species in human endothelial cells. Together, mechanisms underlying neuroprotection include decreased vascular endothelial reactive oxygen species, decreased inflammatory cytokines, improved cerebral blood flow, and restoration of the neurovascular unit.

Also in the same mouse model of VCID, treatment with Ang1-7 (50 or 500 µg/kg/day, s.c.) or the MasR agonist peptide PNA5 (50 or 100 µg/kg/day, s.c.) for 24 days reversed cognitive impairment and significantly decreased a neurodegeneration marker (neurofilament light; NfL) (Hoyer-Kimura et al., 2021). Both doses of PNA5 significantly reduced a proinflammatory marker (TNF-α); only the lower dose of Ang1-7 reduced TNF-α while the higher dose (500 µg/kg/day) resulted in levels higher than mice with myocardial infarction given saline. NfL levels were inversely correlated with cognitive scores and cytokine concentrations.

In a rat model of chronic cerebral hypoperfusion (permanent bilateral occlusion of the common carotid arteries), treatment with Ang1-7 (0.1 or 10 pg/h, osmotic mini pump into the right lateral cerebral ventricle) for 2 weeks significantly alleviated cognitive deficits, as measured by the Morris water maze

(Xie et al., 2014). This neuroprotective effect was associated with increased nitric oxide generation, decreased neuronal loss in the hippocampal CA1, and suppressed astrocyte proliferation in the hippocampus.

Cognitive impairment: In rats subjected to streptozotocin-induced diabetes and cognitive impairment, intracerebroventricular infusion of Ang1-7 for 2 weeks significantly ameliorated cognitive deficits (measured by the Morris water maze), lessened damage to hippocampal synapses, normalized the expression of ACE2 and MasR, and reduced the levels of p-tau (at Ser396, Ser404, and Ser202/Thr205), oligomeric amyloid, soluble amyloid, and insoluble Aβ42 and Aβ40 (Chen et al., 2017). These neuroprotective effects were mediated through MasR activation.

In aged female rats, oral delivery of Ang1-7 via a genetically modified probiotic (Lactobacillus paracasei modified to express Ang1-7; 2 x 10^11 colony-forming units/kg body weight probiotic) 3 times per week for 12 weeks resulted in greater exercise tolerance (longer time to exhaustion) and higher recognition index in the object recognition task (Hernandez et al., 2023). These benefits were not observed in male rats performing exercise and given the probiotic Ang1-7 treatment.

Surgery, especially in older individuals, can lead to cognitive impairment, and this may be mediated in part by the increase in the RAS activity, leading to the disruption of the blood-brain barrier (Mi et al., 2021). In an aged rat model of delayed neurocognitive recovery (after laparotomy), AngII levels were increased while Ang1-7 levels were decreased in the hippocampus. Surgery also significantly downregulated hippocampal Mas receptor expression at 24 hours post-surgery. Treatment with the nonpeptide analog of Ang1-7, AVE0991 (0.9 mg/kg, intranasally, immediately after surgery) significantly ameliorated surgery-induced hippocampus-dependent learning and memory deficits while attenuating neuroinflammation (measured by CD11b, RAGE, HMGB1, TNF-α, and IL-1β). In addition, AVE0991 treatment improved markers of blood-brain barrier integrity (lessened the imbalance between MMP-9 and TIMP-3, modulated occluding expression, and lessened IgG extravasation).

Huntington's disease: In Huntington disease patients, plasma Ang1-7 levels are significantly higher than healthy controls, while no differences were seen in levels of ACE, ACE2, or AngII (Kangussu et al., 2022). However, levels of Ang1-7 varied widely across Huntington disease patients. In a mouse model of Huntington's disease (BACHD mice), Ang1-7 levels were significantly lower in the striatum and hippocampus, but not in the prefrontal cortex. ACE or ACE2 levels were not significantly different in any of those brain regions between these mice and wild-type mice. Also, no differences were found in the levels of ACE, Ang II, ACE2, and Ang1-7 in the plasma of these mice compared with wild-type mice.

Brain injury: Upregulation of the Ang1-7/MasR axis of the RAS has been proposed as a pathway for neuroprotective interventions after brain injury and other brain conditions (reviewed in Annoni et al., 2022). In rodents subjected to subarachnoid hemorrhage, Ang1-7 treatment mitigated inflammatory processes and improved functional outcomes.

In mice subjected to controlled cortical impact injury, Ang1-7 treatment (1.0 mg/kg, i.p.) started 2 hours after injury and continued through day 5 post-injury significantly increased cognitive function and preserved cortical and hippocampal structures by attenuating neuronal loss (Bruhns et al., 2022). Ang1-7 treatment reduced reactive gliosis in treated mouse cortex. Ang1-7 treatment did not significantly change serum levels of proinflammatory mediators post-TBI (IL-6, IL-1β, and TNF-α), partly because they were not detected above baseline levels (reflecting the mild brain injury model). Tau and p-tau levels were altered with Ang1-7 treatment, though the direction of change depended on the brain region. In cortical tissue, Ang1-7 treatment led to higher expression of p-tau and lower expression of tau relative to pre-injury. In the hippocampal tissue, Ang1-7 treatment led to a lower expression of p-tau and higher expression of tau relative to pre-injury baseline.

APOE4 interactions: There have not been any studies evaluating the potential efficacy of Ang1-7 for cognitive decline or dementia in APOE4 carriers versus noncarriers. One meta-analysis of 9 observational studies examining the relationship between APOE status and COVID-19 outcomes reported a significantly higher risk and severity of COVID-19 in APOE4 carriers (OR=1.44 for risk, OR=1.85 for disease progression)(Chen et al., 2023). SARS-CoV-2 infection is achieved through its spike protein binding to ACE2 receptor expressed on host cell membranes. One potential mechanism by which APOE4 increases the risk and severity of COVID-19 is through APOE4-induced downregulation of ACE2 protein expression, leading to decreased conversion of AngII to Ang1-7.

Aging and related health concerns: Clinical evidence is limited, but evidence from laboratory studies suggest potential benefits for cancer, cardiovascular diseases, type 2 diabetes, and ocular diseases.

Types of evidence:

- 3 clinical trials, 2 in cancer patients and 1 in COVID-19 patients
- Numerous laboratory studies

There have been numerous laboratory studies exploring the clinical potential of Ang1-7 in age-related diseases (Machado-Silva et al., 2016), but only a few human clinical trials have reported the effects of Ang1-7 in peer-reviewed journals.

Cancer: MAY REDUCE CYTOPENIAS FROM CHEMOTHERAPY
Myelosuppressive chemotherapy can lead to multilineage cytopenias (reduction of blood cells), while Ang1-7 is a hematopoietic agent that stimulates the proliferation of multipotential and differentiated progenitor cells in cultured bone marrow and human cord blood (Rodgers et al., 2006). In a phase I/II dose-escalation open-label study of 20 patients with newly diagnosed breast cancer, Ang1-7 treatment (100 µg/kg/day) before and after chemotherapy reduced the frequency of grade 2-4 thrombocytopenia, anemia, and grade 3-4 lymphopenia as compared to filgrastim (comparator). Ang1-7 treatment was given daily for 7 days, followed by a 7-day washout period prior to the first cycle of chemotherapy. Two days after chemotherapy, Ang1-7 treatment was given daily for at least 10 days.

In a double-blind randomized controlled trial of 34 patients with ovarian, Fallopian tube, or peritoneal carcinoma receiving chemotherapy (gemcitabine and carboplatin or cisplatin), treatment with the pharmaceutically formulated Ang1-7, TXA-127 (100 µg/kg) produced pharmacodynamic effects on peripheral blood platelet counts and reduced grade 3-4 thrombocytopenia (Pham et al., 2013). These findings suggest that Ang1-7 stimulates thrombogenesis in the bone marrow. There were no differences in outcomes for patients receiving the 300 µg/kg dose of TXA-127 compared to those receiving placebo.

In vitro studies as well as studies in *in vivo* mouse models have shown that Ang1-7 reduces the proliferation of human cancer cells and xenograft tumors by inhibiting cell proliferation and angiogenesis (reviewed in Gallagher et al., 2014 and Machado-Silva et al., 2016).

Cardiovascular diseases: POTENTIAL BENEFIT BASED ON PRECLINICAL STUDIES
Several experimental studies have shown that Ang1-7 enhances cardiac function and reduces lesions after myocardial infarction (reviewed in Machado-Silva et al., 2016). These benefits are likely mediated by the vasodilatory effects of Ang1-7.

Several studies in rodents have also shown therapeutic benefits with Ang1-7 and/or its analogs in perivascular diseases (obstruction of vasculature), including in models of chronic hind-limb ischemia and ischemic stroke (reviewed in Machado-Silva et al., 2016). These treatments resulted in restoration of blood flow, reduction of tissue necrosis, and improvement of body functions.

COVID-19: UNKNOWN
The SARS-CoV-2 enters cells through ACE2, and during this process, ACE2 is phagocytosed and is no longer functional (Singh et al., 2021). This reduction in ACE2 likely decreases levels of Ang1-7 as it is required for the conversion of AngII to Ang1-7. In a double-blind randomized controlled study of 20 patients with severe COVID-19, treatment with the pharmaceutically formulated Ang1-7, TXA-127 (0.5 mg/kg/day, i.v.) for 10 days did not show any significant effects on the primary endpoints of acute kidney injury and/or respiratory failure requiring mechanical ventilation, because these events happened infrequently, making the analysis underpowered (Wagener et al., 2022).

Metabolic syndrome and type 2 diabetes mellitus: POTENTIAL BENEFIT BASED ON PRECLINICAL STUDIES
In a mouse model of diabetes (streptozotocin-induced), treatment with Ang1-7 or its analog, PanCyte, reduced blood glucose and increased blood insulin levels (reviewed in Machado-Silva et al., 2016). A different study in mice showed that Ang1-7 treatment limited peripheral neuropathy in a mouse model of overnutrition. In rats, treatment with a derivative of Ang1-7 reduced body weight gain, halted visceral fat development, reduced blood and liver cholesterol levels, and normalized glucose intolerance and insulin resistance. In rats with insulin resistance (induced by a high-fructose diet), chronic Ang1-7 treatment (100 ng/kg/min, subcutaneously via osmotic pump) improved insulin sensitivity, restored insulin signal transduction, reduced triglyceride levels, and reduced blood pressure (Giani et al., 2009).

Ocular pathologies: POTENTIAL BENEFIT BASED ON PRECLINICAL STUDIES
Sterile eye drops containing Ang1-7 significantly reduced intraocular pressure in a rat model of glaucoma and decreased the degeneration of retina cells in rats with retinopathy (reviewed in Machado-Silva et al., 2016).

Safety: A few small clinical trials have shown that short-term treatment with Ang1-7 is well-tolerated, though long-term safety is not established.

Types of evidence:

- 3 clinical trials, 2 in cancer patients and 1 in COVID-19 patients
- Numerous laboratory studies

In a double-blind randomized controlled study of 20 patients with severe COVID-19, treatment with the pharmaceutically formulated Ang1-7, TXA-127 (0.5 mg/kg/day, i.v.) for 10 days resulted in adverse

effects including cough, headache, and chest discomfort, but the treatment did not result in hypotension or fever (Wagener et al., 2022). There was no difference between the treatment groups on intubation, length of stay, or mortality. Four patients developed acute kidney injury (3 who received TXA-127 and 1 who received placebo; no statistical difference between the groups). No serious adverse events were observed with TXA-127 treatment. This study was terminated early due to the start of an NIH-funded multicenter study of the efficacy of TXA-127 in COVID-19.

In a double-blind randomized controlled trial of 34 patients with ovarian, Fallopian tube, or peritoneal carcinoma receiving chemotherapy (gemcitabine and carboplatin or cisplatin), treatment with TXA-127 (100 or 300 µg/kg) resulted in adverse events that were comparable to placebo (Pham et al., 2013). Nausea, constipation, and fatigue were the most frequently reported events. Two patients randomized to each group (placebo, TXA-127 at 100 µg/kg, and TXA-127 at 300 µg/kg) discontinued the study due to a treatment-emergent adverse event.

In a phase I/II dose-escalation open-label study of 20 patients with newly diagnosed breast cancer, Ang1-7 treatment (2.5 to 100 µg/kg/day) before (7 days) and after (10+ days) chemotherapy did not result in any dose-limiting toxicity (Rodgers et al., 2006). The frequency of adverse events was lower in patients receiving Ang1-7 than in those receiving filgrastim. No patient required modification of chemotherapy due to hematologic toxicity. At a dose of 100 µg/kg/day, Ang1-7 reduced the frequency of grade 2-4 thrombocytopenia, anemia, and grade 3-4 lymphopenia as compared to the comparator, filgrastim.

In spontaneously hypertensive rats, treatment with Ang1-7 (400 ng/kg/min, subcutaneously via an osmotic mini pump) did not affect blood pressure (Stoyell-Conti et al., 2021).

Drug interactions:
Drug interactions have not been documented.

Sources and dosing: Ang1-7 is not currently approved for the treatment of any condition. TXA-127 is a pharmaceutically formulated Ang1-7 and has been used in clinical trials (Wagener et al., 2022). The pilot double-blind randomized controlled trial in 22 severe COVID-19 patients tested a TXA-127 dose of 0.5 mg/kg/day, intravenously.

Because Ang1-7 is a peptide, it is susceptible to degradation and has a short half-life of around 30 minutes (Annoni et al., 2022). Stabilized forms of Ang1-7 are currently under development, including

cyclic Ang1-7, cyclodextrins-included or bioencapsulated Ang1-7, or modified peptides such as PNA5 (Ang-1–6-O-Ser-Glc-NH2), which show greater brain-penetrating properties than Ang1-7.

PanCyte, a functional equivalent of Ang1-7, developed by Tarix Pharmaceuticals, can also cross the blood-brain barrier and has shown neuroprotective benefits in rodent models of ischemic stroke (middle cerebral artery occlusion)(Machado-Silva et al., 2016; US Patent No 9,511,055 B2). The inventors have demonstrated that Ang1-7 is able to ameliorate the symptoms and complications of stroke, even after the treatment is given after the critical period (i.e., golden hour) had passed.

Research underway: There are currently 11 ongoing clinical trials testing Ang1-7 (ClinicalTrials.gov). There are 5 studies in obesity and/or hypertension, 3 in COVID-19, 1 in heart failure, 1 in peripheral arterial disease, and 1 in cardiovascular aging.

Search terms:
Pubmed, Google:

- + cognitive, + dementia, + meta-analysis, + clinical trial, + ApoE4

Websites visited for Angiotensin 1-7:

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

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