U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Apoaequorin. [Updated 2019 Dec 11].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Apoaequorin

Updated: December 11, 2019.

OVERVIEW

Introduction

Apoaequorin is a recombinant protein used as a dietary supplement that is purported to improve memory and verbal learning. Apoaequorin has not been associated with serum enzyme elevations during therapy nor with clinically apparent liver injury.

Background

Apoaequorin is a calcium binding protein found in luminescent jellyfish (Aequorea victoria). When the natural (apo) form of the protein is conjugated with coelenterazine, the resulting protein aequorin has natural bioluminescence when exposed to calcium. For this reason, it has been used as a research molecule to study intracellular physiology and regulation of calcium flux. Recombinant apoaequorin, developed for use in research studies, was subsequently evaluated for its potential to improve memory. The basis for this use of aequorin was its calcium binding characteristics which resembled those of calmodulin, an intracellular protein complex which appears to play a central role in memory. A single trial of oral apoaequorin in patients with memory problems found no overall differences in changes in measures of verbal learning in comparison to placebo, but slightly greater improvements were reported in a subset of patients with normal cognitive test values at baseline. These findings were questioned later because of the lack of evidence that apoaequorin is absorbed orally or can cross the blood-brain barrier. Nevertheless, apoaequorin is marketed as a dietary supplement that supports brain health and helps with aging-related memory loss. It has been used off label in patients with amyotrophic lateral sclerosis and multiple sclerosis. Apoaequorin is available in tablets of 10, 20 and 40 mg under the brand name Prevagen. It has not been approved by the FDA as therapy of memory loss or neurologic illnesses. Side effects were not reported in the few prospective studies that have been published. Adverse events reported to the sponsor have been rare but have included headache, nausea, constipation, edema and hypertension. There have been anecdotal reports of serious adverse events in persons with multiple sclerosis taking apoaequorin including hypotension and depression with suicidal ideation.

Hepatotoxicity

Apoaequorin is considered generally safe and without major adverse effects. In the human studies that have been published there were no reports of serum enzyme elevations occurring during therapy and no mention of serious adverse events or hepatotoxicity.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism by which apoaequorin might cause hepatotoxicity is unclear. Indeed, there is little evidence that apoaequorin is absorbed orally, most proteins being broken down in the stomach and intestines to individual amino acids or short polypeptides. Allergic reactions can occur with proteins taken orally but have not been reported with apoaequorin. The possibility of mislabeling or adulteration with hepatotoxic natural products is always an issue in commercial supplements.

Drug Class: Herbal and Dietary Supplements

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Apoaequorin – Prevagen®

DRUG CLASS

Herbal and Dietary Supplements

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Apoaequorin	50934-79-7	Recombinant Protein	Not Applicable

ANNOTATED BIBLIOGRAPHY

References updated: 11 December 2019

Abbreviations used: HDS, herbal and dietary supplements; ALS, amyotrophic lateral sclerosis.

Zimmerman HJ. Unconventional drugs. Miscellaneous drugs and diagnostic chemicals. In, Zimmerman, HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999: pp. 731-4.

(Expert review of hepatotoxicity published in 1999; several herbals are discussed, including comfrey, germander, chaparral leaf, skullcap and valerian, but not apoaequorin).

Seeff L, Stickel F, Navarro VJ. Hepatotoxicity of herbals and dietary supplements. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 631-58.

(Review of hepatotoxicity of herbal and dietary supplements [HDS]; apoaequorin is not discussed).

No authors listed. Apoaequorin. In, Natural medicines: comprehensive database. Available at: https://naturalmedicines.therapeuticresearch.com/databases/food,-herbs-supplements/professional.aspx?productid=1486.

(Fact sheet on natural products mentions that apoaequorin is a protein that given orally is purported to improve cognitive function, memory and sleep quality, but that published studies do not adequately support its effectiveness).

Shimomura O. A short story of aequorin. Biol Bull 1995; 189: 1-5. 7654844

(Story of the discovery of aequorin using extracts of the light organ granules of Jellyfish [Aequorinae victoria] and the finding that the luminescence required calcium).

Schiano TD. Hepatotoxicity and complementary and alternative medicines. Clin Liver Dis 2003; 7: 453-73. 12879994

(Comprehensive review of herbal associated hepatotoxicity; apoaequorin is not listed as causing hepatotoxicity).

Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver transplantation for acute liver failure from drug-induced liver injury in the United States. Liver Transpl 2004; 10: 1018-23. 15390328

(Among ~50,000 liver transplants reported to UNOS between 1990 and 2002, 270 [0.5%] were done for drug induced acute liver failure, including 7 [5%] attributed to herbal medications, but none to apoaequorin).

Shimomura O. The discovery of aequorin and green fluorescent protein. J Microsc 2005; 217(Pt 1): 1-15. 15655058

(History of the discovery and characterization of aequorin and green fluorescent protein for which Dr. Shimomura was awarded the Nobel Prize in Chemistry in 2008).

Payne AG. Experimental regimen targeting the ependyma slows disease progression in four patients with amyotrophic lateral sclerosis. Med Hypotheses 2009; 72: 548-50. 19200662

(The author hypothesizes that amyotrophic lateral sclerosis is due to production of neurotoxins by cerebrospinal fluid producing brain cells, in support of which he describes 4 patients with ALS who experienced relatively less disease progression when treated with a regimen including a medium chain triglyceride diet, lithium, ubiquinone, noni juice, turmeric extract, glutathione and, in two instances, apoaequorin [20 mg every 2-3 hours]).

Teschke R, Wolff A, Frenzel C, Schulze J, Eickhoff A. Herbal hepatotoxicity: a tabular compilation of reported cases. Liver Int 2012 32: 1543-56. 22928722

(A systematic compilation of all publications on the hepatotoxicity of specific herbals identified 185 publications on 60 different herbs and supplements, but apoaequorin was not listed).

Bunchorntavakul C, Reddy KR. Review article: herbal and dietary supplement hepatotoxicity. Aliment Pharmacol Ther 2013; 37: 3-17. 23121117

(Systematic review of literature on HDS associated liver injury; does not mention apoaequorin).

Moran DL, Marone PA, Bauter MR, Soni MG. Safety assessment of Apoaequorin, a protein preparation: subchronic toxicity study in rats. Food Chem Toxicol 2013; 57: 1-10. 23470325

(Toxicology study of recombinant apoaequorin in rats found no evidence of toxicity even at doses [667 mg/kg daily] far in excess of what is used in humans [20 mg daily]).

ALSUntangled Group. ALSUntangled no. 18: apoaequorin (Prevagen). Amyotroph Lateral Scler Frontotemporal Degener 2013; 14: 78-9. 23030514

(An assessment of the efficacy and safety of apoaequorin by a scientific advisory group for an ALS patient group concluded that there was insufficient data to suggest that it was beneficial in slowing the progression of ALS and that two patients with multiple sclerosis have reported serious adverse events while taking it [hypotension, depression]).

Navarro VJ, Barnhart H, Bonkovsky HL, Davern T, Fontana RJ, Grant L, Reddy KR, et al. Liver injury from herbals and dietary supplements in the U.S. Drug-Induced Liver Injury Network. Hepatology 2014; 60: 1399-408. 25043597

(Among 85 cases of HDS associated liver injury enrolled in a US prospective study between 2004 and 2013, none were attributed to an apoaequorin-containing product).

García-Cortés M, Robles-Díaz M, Ortega-Alonso A, Medina-Caliz I, Andrade RJ. Hepatotoxicity by dietary supplements: a tabular listing and clinical characteristics. Int J Mol Sci 2016; 17. pii: E537. 27070596

(Listing of published cases of liver injury from HDS products; does not mention or discuss apoaequorin).

Moran DL, Underwood MY, Gabourie TA, Lerner KC. Effects of a supplement containing apoaequorin on verbal learning in older adults in the community. Adv Mind Body Med 2016; 30: 4-11. 26878676

(Among 218 adults with self-reported memory concerns treated with apoaequorin or placebo for 90 days, the number of items correctly recalled was similar in both groups, although small differences were found in a subset of persons with normal recall at baseline).

Spence J, Chintapenta M, Kwon HI, Blaszczyk AT. A brief review of three common supplements used in Alzheimer's disease. Consult Pharm 2017; 32: 412-4. 28701253

(Review of the efficacy and safety apoaequorin, Cerefolin NAC and omega-3-fatty acids as therapy for Alzheimer's disease; does not mention ALT elevations or hepatotoxicity with any of the 3 and concludes that "meaningful evidence is lacking" for their efficacy).

Brown AC. Liver toxicity related to herbs and dietary supplements: online table of case reports. Part 2 of 5 series. Food Chem Toxicol 2017; 107 (Pt A): 472-501. 27402097

(Description of an online compendium of cases of liver toxicity attributed to HDS products does not mention or discuss apoaequorin).