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.

Sterubin

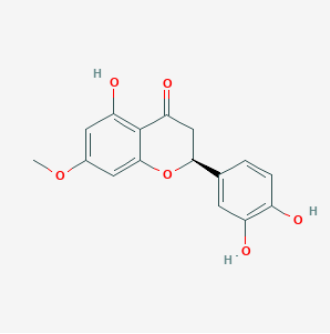
Evidence Summary

Cell culture studies suggest sterubin has anti-oxidant, anti-inflammatory, anti-amyloid, and neurotrophic effects, but no in vivo or human studies exist to date. A topical application may darken gray hair/beard.

Neuroprotective Benefit: Based on cell culture studies, sterubin has anti-oxidant, anti-inflammatory, anti-amyloid, and neurotrophic effects. No human or in vivo studies have tested its potential for neuroprotection.

Aging and related health concerns: There is no evidence that sterubin protects against age-related illnesses, though a few studies suggest a topical treatment may darken gray/white hair and beard.

Safety: Safety of sterubin treatment is not established. Topical treatment with Yerba santa extract or sterubin in a small number of people have shown that there was no darkening of the skin despite the beard/hair regaining pigmentation.

Availability: not available; research grade only	**Dose**: not established	**Chemical formula:** $C_{16}H_{14}O_6$ **MW**: 302.28  Source: PubChem
Half life: not documented	**BBB**: not documented	
Clinical trials: none	**Observational studies**: none	

What is it? Sterubin is a flavanone present in a shrub called Yerba santa (*Eriodictyon californicum; Eriodictyon angustifolim*), which has been used by native California tribes to treat respiratory ailments (cough, cold, asthma, bronchitis), fever, headaches, wounds, and joint pain from rheumatism (Drugs.com; WebMD.com). Sterubin was identified through an age-associated phenotypic screen for Alzheimer's disease drug candidates using a library of 400 plant extracts (Fischer et al., 2019). Yerba santa has been used in tea and topically to manage bruises and rheumatic pain (Drugs.com). Yerba santa is also used to mask the bitter taste of certain medications (WebMD.com).

Neuroprotective Benefit: Based on cell culture studies, sterubin has anti-oxidant, anti-inflammatory, anti-amyloid, and neurotrophic effects. No human or *in vivo* studies have tested its potential for neuroprotection.

Types of evidence:

- 2 *in vitro* 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:
Sterubin was identified through an age-associated phenotypic screen for Alzheimer's disease drug candidates using a library of 400 plant extracts (Fischer et al., 2019). A combination of phenotypic screening assays reflecting multiple age-associated neurotoxicity pathways were used: oxidative glutamate toxicity, protection against energy (ATP) depletion, intracellular amyloid toxicity, inhibition of inflammation mediated by microglial activation, and differentiation of rat PC12 cells. The library of plant extracts was chosen to maximize the potential for hits while minimizing the identification of toxic compounds by focusing only on plants with a history of use as traditional medicine or observational association with decreased disease risk.

The oxidative glutamate toxicity assay identified 9 plant extracts out of 400 that showed protection, one of which was the Yerba santa extract (Fischer et al., 2019). Yerba santa was further analyzed by HPLC fractionation and the fraction that had the highest cell survival (~50% survival) was selected--other fractions did not show any significant protection. From this fraction, 2 flavonoids were identified--homoeriodictyol and sterubin. Sterubin was found to show activities similar to the Yerba santa active fraction, whereas homoeriodictyol did not. Sterubin was confirmed to be highly effective in all of the assays.

A follow-up study also confirmed that the protective properties of different Eriodictyon species correlated with the amount of sterubin, but not with eriodictyol or homoeriodictyol, indicating that sterubin is the major active compound in these species (Maher et al., 2020). The authors also noted their surprise at how stable sterubin and other compounds were in specimens that dated back to 1878.

Compared to fisetin, sterubin has a higher hydrophilicity (ClogP) value, a smaller topological polar surface area, and one less hydrogen bond donor (Fischer et al., 2019). These properties make sterubin potentially more cell membrane permeable and more potent than fisetin. It also meets physiochemical criteria to be a viable CNS drug candidate. However, no studies to date have examined sterubin metabolites and pharmacokinetics *in vivo*.

Antioxidant activity: IN CELL CULTURE, INCREASES GSH AND NRF2, DECREASES ROS, CHELATES IRON
Sterubin dose-dependently increased levels of the antioxidant glutathione (GSH) in control cells and maintained the levels of GSH in cells treated with glutamate (Fischer et al., 2019). Sterubin dose-

dependently protected against two inducers of ferroptosis and reduced glutamate-induced reactive oxygen species (ROS) production. Sterubin also significantly reduced the basal levels of ROS and was effective against cell death induced by either H_2O_2 or t-butyl hydroperoxide with EC_{50} of ~ 1 µM. Sterubin was also an effective iron chelator.

Two transcription factors contribute to the upregulation of GSH, Nrf2 and ATF4. In cell culture, sterubin dose-dependently increased nuclear Nrf2 levels to a maximum of 6-fold at 5 µM (Fischer et al., 2019). This increase was seen within 30 min of sterubin treatment and remained for up to 6 hours. ATF4 plays an important role in the maintenance of GSH levels in neurons and sterubin dose-dependently increased nuclear ATF4 levels to a maximum of 3-fold at 5 µM. The increase in nuclear ATF4 was seen within 30 min of treatment and remained for up to 6 hours. Sterubin also increased the levels of p62 (by 22.7-fold) and heme oxygenase 1 (HO-1) (by 4.1-fold), two proteins involved in protection against oxidative stress that are known to be regulated by Nrf2.

Anti-inflammatory activity: IN CELL CULTURE, DECREASES INFLAMMATORY CYTOKINES
Sterubin had potent anti-inflammatory activity in BV-2 microglial cells (Fischer et al., 2019). The BV-2 cells were treated with different doses of sterubin in the presence of LPS and levels of NO, IL-6, IL-1β and TNFα were measured in culture supernatants and levels of iNOS and COX2 were assessed in cell extracts. Sterubin dose-dependently reduced the production of NO, IL-6 and IL1β as well as the levels of both iNOS and COX2. A smaller effect was seen on the induction of TNFα. Sterubin also dose-dependently increased nuclear Nrf2 and ATF4 levels in the BV-2 microglial cells, suggesting that Nrf2 may play a key role in the anti-inflammatory effects of sterubin.

Protection against amyloid toxicity: IN CELL CULTURE, INHIBITS Aβ TOXICITY
In cell culture, sterubin is effective at inhibiting intracellular Aβ toxicity with an EC_{50} of 0.8 µM (Fischer et al., 2019). Interestingly, the EC_{50} value of sterubin was 4-times better than that of fisetin (EC_{50} of 3.3 µM).

Neuronal differentiation: IN CELL CULTURE, INDUCES NEURITE OUTGROWTH
In rat PC12 cells, sterubin induced neurite outgrowth (Fischer et al., 2019). The catechol B-ring with phenolic hydroxyls on sterubin may be important for its neurotrophic activities. Sterubin, eriodictyol, and fisetin all contain a 3',4'-dihydroxyl groups on the catechol B-ring and they have EC_{50} values less than 5 µM for phenotypic screening assays. In contrast, homoeriodictyol, which contains a 3'-methoxy 4'-hydroxy on the B-ring, is inactive (EC_{50} over 10 µM).

APOE4 interactions: Unknown.

Aging and related health concerns: There is no evidence that sterubin protects against age-related illnesses, though a few studies suggest a topical treatment may darken gray/white hair and beard.

Types of evidence:

- 1 clinical study of Yerba santa extract topical treatment
- 1 case study of topical sterubin treatment
- A few laboratory studies

Cancer: NO BENEFIT IN CELL CULTURE
In a cell culture model of colon cancer (HCT colon cancer cell line), sterubin did not show cytotoxicity (Gordo et al., 2012). The GI_{50} value (concentration for 50% maximal inhibition of cell proliferation) was over 20 µg/ml.

Hair pigment regeneration: TOPICAL APPLICATION MAY DARKEN GRAY HAIR/BEARD
In humans: In a clinical study of male volunteers, topical application of a Yerba santa (*Eriodictyon angustifolim*) extract to the beard for 9 months significantly inhibited the rate of increase in gray beard compared to volunteers who received no treatment or the solvent control (50% ethanol)(Taguchi et al., 2020). In addition to the protective effects against beard graying, there was darkening of beard in some cases with the extract application, noticeable within 4 weeks post-application.

In the same study, 10 volunteers were given topical application of the Yerba santa (*Eriodictyon angustifolim*) extract to the scalp for 24 weeks. Eight out of ten subjects showed an improvement in the gray hair ratio. The gray hair ratio gradually decreased -0.7%, -1.3%, and -3.4%, at 4, 12, and 24 weeks, respectively. A significant hair thickening effect was also observed in extract-treated hair.

They then analyzed 1-cm^2 scalp areas containing both gray hair shaft representing a recently formed gray hair (indicating loss of melanin synthesis activity) and completely unpigmented hair shafts (indicating a loss of mesenchymal stem cells; MSCs). When the *Eriodictyon angustifolim* extract was applied to a subject, gray hair became re-pigmented after 8 days, whereas white unpigmented hair (lacking MSCs) remained unchanged after 9 months of daily extract application.

After one month of *Eriodictyon angustifolim* extract application to human beard follicles and hair

follicles, these follicles were plucked for gene expression analysis (Taguchi et al., 2020). Increased expression of genes associated with melanin production, melanosome transport, WNT signaling, and anti-apoptotic signaling was detected, while the expression of dickkopf 3 (DKK3), which has a WNT-inhibitory effect, was decreased.

In a single subject who received a topical application of 0.1 w/v% sterubin to the cheek area for 2-4 weeks, pigmentation was restored in gray beard (Taguchi et al., 2018).

Preclinical data: Preclinical studies also support efficacy of Yerba santa and sterubin in repigmentation of hair/beard. In mice with dorsal skin excised, the rate of hair regeneration on day 80 was 70.6% with sterubin treatment but 20.5% in control (no drug) (Taguchi et al., 2019). Furthermore, the ratio of pigmented hair regeneration was 47.1% with sterubin treatment but 0.0% with no treatment. Sterubin activated melanocyte stem cells to regenerate pigmented hair in comparison with other flavonoids and controls.

Hair follicles can show regenerative potential even after turning white, and pigmented hair can be maintained by manipulating follicular melanocytes. If melanocytes are present in the hair matrix, gray hair could become pigmented hair through expression of melanin production-related genes in melanocytes. Microphthalmia-associated transcription factor (MITF) is the master regulator of pigmentation genes. MITF can be activated by signaling through WNT/β-catenin, the melanocortin 1 receptor, endothelin, and Kit receptor tyrosine kinase (Taguchi et al., 2020).

In a human melanoma cell line (HMVII), sterubin treatment showed 1.47- to 1.65-fold concentration-dependent increase in melanin content after 7 days of exposure (Taguchi et al., 2018). Sterubin treatment also resulted in nuclear translocation of β-catenin, which is indicative of WNT signaling activation, and nearly 1.4-fold increase in nuclear MITF expression and 4.6-fold increase in cytoplasmic tyrosine kinase expression. When normal human epidermal keratinocytes were exposed to sterubin, cell viability under X-ray irradiation was significantly increased while DNA damage was decreased, as measured by the decreased phosphorylated H2AX foci per cell, which is indicative of reduced DNA damage after irradiation. Sterubin treatment also significantly suppressed the radiation-induced generation of reactive oxygen species to levels comparable to non-irradiated control cells. Sterubin treatment for 1 hour before irradiation significantly prevented severe deformation of the mitochondrial mass in normal human epidermal keratinocytes.

Consistent with the sterubin data, *Eriodictyon angustifolium* extract also increased melanin synthesis and WNT, MITF, and tyrosine kinase expression in a human melanoma cell line (Taguchi et al., 2020). *Eriodictyon angustifolium* extract exposure resulted in the nuclear translocation of β-catenin, which is indicative of the activation of WNT signaling. In addition, increases in nuclear MITF expression and cytoplasmic tyrosine kinase expression were shown after exposure to the *Eriodictyon angustifolium* extract. The extract also showed a suppressive effect on radiation-induced DNA damage and cell death in normal human epithelial keratinocytes. Pre-exposure of normal human epidermal keratinocytes to the *Eriodictyon angustifolium* extract also resulted in reduced DNA damage after irradiation. The extract also rescued normal human epidermal keratinocytes from X-ray-induced cell death. The extract significantly suppressed the radiation-induced generation of reactive oxygen species. Pre-treatment with the *Eriodictyon angustifolium* extract also prevented severe deformation of mitochondrial mass in normal human epidermal keratinocytes.

Safety: Safety of sterubin treatment is not established. Topical treatment with Yerba santa extract or sterubin in a small number of people have shown that there was no darkening of the skin despite the beard/hair regaining pigmentation.

Types of evidence:

- 1 clinical study of Yerba santa extract topical treatment
- 1 case study of topical sterubin treatment

Yerba santa has been used in tea and medicinally but the safety profile is not well-documented (Drugs.com). No clinical trials have investigated the safety of sterubin treatment for any indication.

In an open-label study of 10 volunteers who applied Yerba santa (*Eriodictyon angustifolium*) extract to the beard or scalp for 9 months, darkening of the skin surrounding the beard or scalp was not observed (Taguchi et al., 2020). Other adverse events were not reported.

In a case report of one subject who received a topical application of 0.1 w/v% sterubin to the cheek area for 2-4 weeks, there was no darkening of the skin (Taguchi et al., 2018). Other adverse events were not reported.

Drug interactions: Drug interactions with sterubin or Yerba santa are not well documented (Drugs.com). Yerba santa may have moderate interactions with lithium due to its diuretic effects, potentially decreasing how well the body metabolizes lithium (WebMD.com).

Sources and dosing: Sterubin is a flavanone present in a shrub called Yerba santa (*Eriodictyon californicum*). The dosage of sterubin is not established. Classical use of Yerba santa leaves as an expectorant is at 1 g doses (Drugs.com).

Research underway: There are currently no ongoing clinical trials testing sterubin for dementia or age-related diseases. There are currently no NIH-funded programs investigating sterubin specifically.

Search terms:
Pubmed, Google:

- Sterubin, 7-O-Methyleriodictyol, and Yerba santa

Websites visited for sterubin, 7-O-Methyleriodictyol, or Yerba santa:

- Clinicaltrials.gov (0)
- NIH ProjectReporter (0)
- Examine.com (0)
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca (0)
- Labdoor.com (0)
- Cafepharma (0)
- Pharmapro.com (0)

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