SAFETY PROFILE OF PURIFIED LARREA TRIDENTATA LEAF RESIN EXTRACT ALONE AND IN COMBINATION WITH ASCORBIC ACID

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Desert creosote bush, Larrea tridentata (Cov.), is a shrubby plant that dominates desert areas of the Southwest U.S. This plant has long been used in folk medicine by Native Americans and European settlers to treat various health conditions.

Employing an in vitro hepatotoxicity model based on precision cut rat liver slices, Larrea leaf resin extract processed with ascorbic acid was no more toxic to liver tissue than other generally recognized as safe (GRAS) food substances such as cinnamon oil and clove oil. Additionally, when the processed Larrea leaf resin extract is formulated in a 1:5 ratio with ascorbic acid, this combination is substantially safer than cinnamon oil or clove oil and may actually be hepatoprotective.

An acute toxicity study, compliant with the principles of the Good Laboratory Practice Regulations of the United States Food and Drug Administration, further confirmed the safety of purified Larrea leaf resin formulated in a 1:5 ratio with ascorbic acid. No adverse effects such as, toxic symptoms, illness, deaths, weight changes or toxic gross pathological changes to liver or kidneys were noted following a 2,000 milligram/kilogram dose of a dietary supplement formulation containing this mixture of Larrea leaf resin extract and ascorbic acid. This experimental dosage represents the highest dose that can be given to rats safely and is the limit dose suggested in the international guidelines for acute toxicity testing.

Larrea tridentata; an Abundant and Natural Chemical Factory

- Dominant plant in the southwest US deserts
- 40 million acres
- Plants can be >10,000 years old
- Approximately 5-10% (w/w) extractable leaf resin

***Larrea tridentata* (DC.) Cov.**

Purified Larrea Leaf Resin Extract

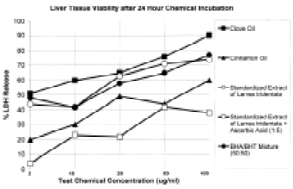
- Commercial process
  - Whole, dried foliage extracted with FCC-grade organic solvents + PS80
  - Clarification
  - FCC-grade ascorbic acid filtration bed
  - Solvent evaporated
  - Resin recovered, standardized, blended

Historical Uses of Larrea

- The "Medicine Chest" plant
  - Pima, Papago, Yavapai, Hualapai, Coahuilla, Paiute, Shoshoni, etc.
  - Skin disorders, arthritis, rheumatism, headache, fever, asthma, congestion, chest infections, bowel problems, venereal disease, cancer, tuberculosis, etc.

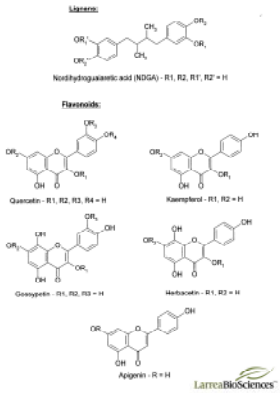
In vitro hepatotoxicity model*

- Purified Larrea leaf resin
- GRAS natural phenolics cinnamon oil (LD50 = 2.65 g/kg) and clove oil (LD50 = 1.93 g/kg)
- Synthetic phenolics BHA/BHT (50:50)
- Purified Larrea leaf resin plus 5x ascorbic acid



* University of Arizona, School of Medicine (Tucson, AZ)

- External leaf resin from *Larrea tridentata*
- Approximately 50:50 flavonoids and lignans
- Solubility - MeOH, EtOH, propylene glycol, acetone
- Insoluble - water, petroleum ether



GLP oral toxicity study*

- Sprague-Dawley rat model
- Formulation with Larrea resin/ascorbic acid (1:5)
- Maximum dose (2000mg/kg) used
- 14 day post examination period
- "no adverse effects"
  - No toxic symptoms
  - No illness
  - No mortality
  - No weight changes
  - No toxic gross pathological changes to liver or kidneys

* American Institute for Biosocial and Medical Research, Inc. (Tacoma, WA) and Pharmaceutical Control and Development Laboratory Co., Ltd. (Budapest)

Conclusions:

- **Purified Larrea leaf resin extract, containing flavonoids and lignans, has low toxicity**
- **Intermediate between cinnamon oil and clove oil, both GRAS food substances**
- **When formulated with 5:1 ratio of ascorbic acid and purified leaf resin has lower toxicity than cinnamon oil or clove oil and may actually be hepatoprotective**
- **GLP acute toxicity study shows no adverse effects at maximum dose – equivalent to 270 capsules/150 lb. (68 kg) man (135x maximum)**

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