NTP
National Toxicology Program

Report on Carcinogens Goldenseal Root Powder Concept Review

Diane L. Spencer, M.S.
Office of the Report on Carcinogens
National Institute of Environmental Health Sciences

Board of Scientific Counselors Meeting
April 17, 2014

What is goldenseal?

Hydrastis canadensis

Wild, slow-growing perennial herb whose root-like yellow underground stems (rhizomes) are dried and ground into a powder

Herbal remedy for a variety of conditions

How are people exposed to goldenseal root powder in the United States?

Currently used as herbal remedy

- Digestive disorders, colds, respiratory, skin, other infections
- Has drying effects on mucous membranes
- Ingested (capsule, tablet, tea or water) or used dermally as a paste

Regulated as a dietary supplement under the Dietary Supplement Health and Education Act of 1994

Evidence for widespread exposure

- Databases show hundreds of products on the market contain goldenseal
- Ranked in top 20 botanical dietary supplements sold in the United States

Rationale

Widespread use as herbal remedy, therefore potential for substantial exposure to U.S. population

There is an adequate database for review:

- NTP Technical Report (2010) – two-year rodent bioassay
- IARC (2013) – Classified goldenseal root powder as *possibly carcinogenic to humans* (Group 2B)

Cancer Studies

Humans: No epidemiological studies

Experimental animals:

- NTP Technical Report 562 (2010) 2-year bioassay; route: feed
  - Rats (F344/N)
    - Hepatocellular adenoma in males and females
    - Hepatocellular adenoma or carcinoma in males
  - Mice (B6C3F1)
    - Hepatoblastoma and multiple hepatocellular adenoma in males
    - No evidence of carcinogenic activity in females

Studies on Metabolism

Active ingredients

- Isoquinoline alkaloids
- Effects primarily attributed to berberine and hydrastine

Available database

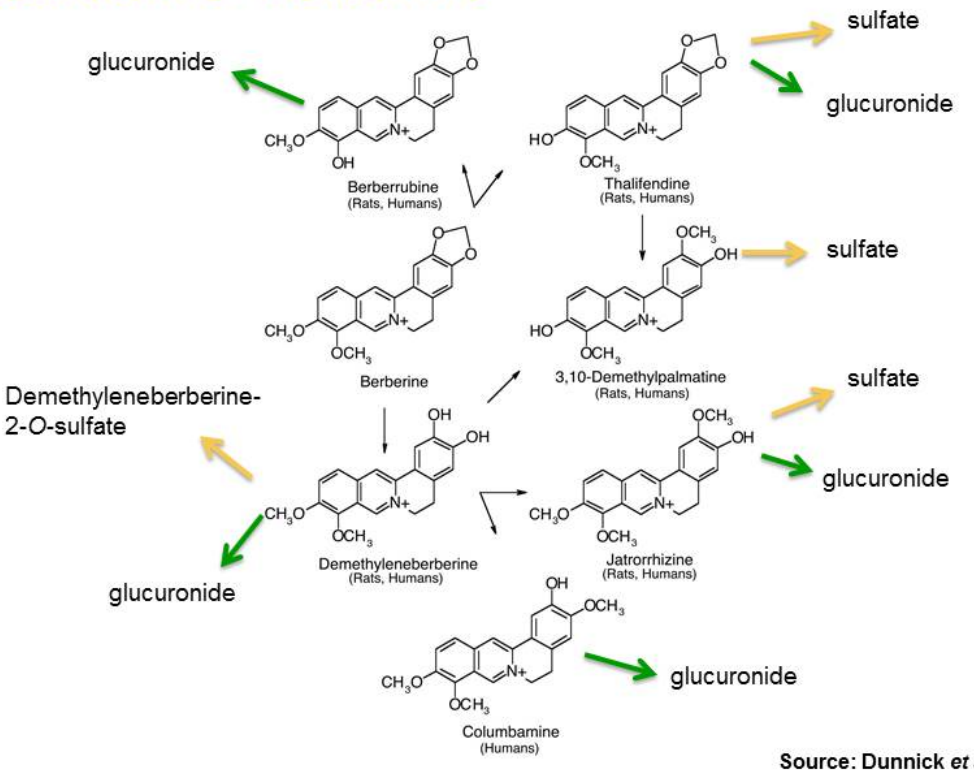
- Studies mostly on berberine in rodents
- Few studies on goldenseal

Metabolism studies of berberine *in vivo*, mostly in rats or rabbits (oral or i.v.); some in humans (ingestion); several *in vitro*

- Absorbed from gastrointestinal tract, distributed to liver; metabolites have been identified from urine and bile

Metabolism of berberine qualitatively similar in rodents and humans

Metabolism of Berberine



Source: Dunnick *et al.* (2011)

Mechanistic Studies

Several mechanistic studies, both *in vitro* and *in vivo*, have been identified for goldenseal or berberine

Berberine is a topoisomerase II inhibitor which may cause

- DNA damage
- Other types of genotoxic effects

Berberine inhibits Cytochrome P450 enzymes in exposed humans

- Potential pharmacokinetic interactions for goldenseal with conventional medications

Issues

One public comment was received in response to Federal Register notice (September 20, 2013) of nomination

- Raised issue regarding significance of hepatocellular carcinoma observed in the male rat in the NTP bioassay
- Use of goldenseal root powder in people is short-term

Reduced availability of wild goldenseal may lead to a change in formulation

- Overharvested and loss of woodland habitats
- Increase in commercial cultivation
- Formulation may vary: not same amounts or types of alkaloids, and substituted products may not affect the body in the same way

Key Scientific Questions and Issues

What is the level of evidence (sufficient or not sufficient) for the carcinogenicity of the goldenseal root powder from the studies in experimental animals?

- If sufficient, what are the target tissue sites?

What are the potential mechanisms by which goldenseal root powder may cause cancer?

- Is there evidence to support biological plausibility for cancers of the liver in experimental animals and humans?

Are the active components of goldenseal, e.g., berberine or hydrastine, directly responsible for the observed results?

Proposed Approach: Scientific Input

Monograph planning team

- NTP staff and technical experts
- Relevant expertise on chemistry, metabolism, human exposure and uses of herbals/metabolites
- Help identify relevant literature and review protocol and key sections of draft monograph

Protocol

- Literature search strategy (exclusion/inclusion criteria)
- Approach for evaluating the quality of experimental animal studies

Proposed Approach: Public Input

Webpage

- RoC documents (e.g., concept, protocol, monograph) related to the review of the substance
- Input box
- Information on public meetings
- Public comments

Public input

- Multiple opportunities for comment
- Solicited throughout review process
  - Nomination, concept, monograph
  - Announced via FR notice, NTP listserv, posted on ORoC website

BSC Review Questions

1. Comment on whether there appears to be evidence of past and/or current exposure to people living in the U.S.

2. Comment on whether the extent and nature of the scientific database appears to be adequate to support a RoC evaluation.

3. Advise as to whether the relevant scientific issues are identified. Are you aware of any other scientific issues that need to be considered during the evaluation?

4. Comment on the proposed approach for obtaining scientific and public input in development of the evaluation.

5. Rate the overall significance and public health impact of this evaluation as low, moderate, or high. NTP will use this rating in assessing the relative priority of evaluations of RoC candidate substances.

6. Provide any other comments you feel staff should consider in developing this evaluation.

Isoquinoline Alkaloids

- Berberine – researched the most; up to ~ 6% in goldenseal
- Hydrastine
- Berberastine
- Hydrastinine
- Tetrahydroberberastine
- Canadine
- Canalidine