



## NTP Botanical Dietary Supplements Program

### What are botanical dietary supplements?

Botanical dietary supplements, sometimes called herbals or herbal dietary supplements, are products made from plants. The Food and Drug Administration (FDA) defines dietary supplements, in part, as products taken by mouth that contain a “dietary ingredient,” which could be vitamins, minerals, amino acids, herbs, botanicals, or other substances intended to supplement a diet. Dietary supplements may be found in many forms, such as tablets, capsules, gummies, liquids, or powders.

The market for these products is large. According to the American Botanical Council, U.S. consumers spent \$12.4 billion on herbal dietary supplements in 2021.<sup>1</sup>

Not all products from plant sources, which are sold in stores and online, are safe. The safety of a botanical depends on many factors, such as its chemical structure, how it works in the body, how it is prepared, and the dose taken. These supplements may contain active ingredients with strong biological effects that may interact with over-the-counter and prescription drugs.

**If you become ill or have other adverse health events related to a dietary supplement, contact the FDA Safety Reporting Portal at [www.safetyreporting.hhs.gov](http://www.safetyreporting.hhs.gov).**

### Why is the National Toxicology Program (NTP) studying botanical dietary supplements?

The scientific evidence available on the safety of different botanical supplement ingredients varies, partly because product safety testing is not required by the FDA. Federal law also does not require dietary supplements to be tested for effectiveness before they are marketed. The FDA regulates dietary supplements under a different set of regulations than those covering foods and conventional drugs.<sup>2</sup>

Studying the potential effects of botanical dietary supplements has several challenges. One challenge is that botanical dietary supplements typically contain a complex mixture of ingredients. Also, the complexity of the ingredients, including the number of components within them, make it difficult to identify and link a specific component to a specific health effect.



Growing, harvesting, and processing conditions can affect the chemical makeup of a botanical supplement, leading to challenges in manufacturing identical product batches after batch. Possible product contaminants (e.g., heavy metals, microbes, undeclared ingredients, or pesticides), either accidental or intentional, should be determined as part of routine quality control as these factors can affect product safety.

### How does NTP evaluate botanical dietary supplements?

NTP characterizes the chemical and physical composition of botanical dietary supplements through its testing program. NTP conducts cell-based studies to better understand potential effects of supplements. It also conducts toxicology studies in animal models to understand what happens after a supplement enters the body.

In toxicity testing, NTP conducts studies of short-term exposure to high doses, long-term exposure to lower doses, or other combinations of conditions. NTP also examines toxicities to certain body functions, including reproductive, neurological, cardiovascular, and immune systems. Some studies focus on determining the potential for harmful health effects, such as cancer.





## What do NTP findings mean for me?

Public concern about botanical dietary supplements includes questions about labeling, product quality, health benefits, and risk of harmful effects. NTP studies offer scientific data that can inform decisions by health care providers, government regulators, and consumers. The following examples highlight how NTP's work can improve public use of botanical dietary supplements.

- **Vinpocetine** – This synthetic compound is found in dietary supplements marketed for uses such as improvement of brain function, including to improve memory and focus. NTP studies found harmful reproductive effects in animals exposed to vinpocetine, raising concerns about potential effects on pregnant women and their unborn children. Based on these findings, in 2019, the FDA advised companies marketing vinpocetine products to include a warning on the label for women of childbearing age to avoid vinpocetine because it may cause miscarriage or harm fetal development.<sup>3</sup>
- **Aloe vera** – Applying aloe vera gel to the skin is not likely to cause harm. But some people consume aloe vera to aid their digestive system or relieve constipation. An NTP study in rats found that consuming whole leaf extracts of aloe in drinking water leads to tumors of the large intestine.<sup>4</sup> The study gives cause for serious concern because it may relate to human health. Additional questions to be answered include what products containing aloe vera are in the marketplace, what are the specific active compounds in those products, and what are the patterns of human exposure.
- **Green tea extract** – Green tea is a popular beverage worldwide. However, green tea extract, which is often used in weight loss supplements, is different. It contains high levels of certain chemicals, such as epigallocatechin gallate. Green tea extract is associated with liver toxicity in animal and human studies, including NTP studies. Information from these studies led the U.S. Pharmacopeia to require a label on certain products about possible liver injury and caution that those products should not be taken on an empty stomach.<sup>5</sup>

## Ongoing NTP studies

Botanical Dietary Supplements Currently Studied by NTP	
<b>Echinacea Purpurea</b>	Native to the U.S. and southern Canada, this plant is used fresh or dried to make teas, juice, extracts, or other preparations. More information can be found at <a href="https://doi.org/10.22427/NTP-DATA-DTXSID0031265">https://doi.org/10.22427/NTP-DATA-DTXSID0031265</a> .
<b>Garcinia Cambogia</b>	Often grown for its fruit, which is used for cooking, food preservation, and as a dietary aid. More information can be found at <a href="https://doi.org/10.22427/NTP-DATA-DTXSID8040191">https://doi.org/10.22427/NTP-DATA-DTXSID8040191</a> .
<b>Valerian</b>	A plant native to Asia and Europe, but also found in North America, its root and underground stems are made into capsules, tablets, liquid extracts, and teas. More information can be found at <a href="https://doi.org/10.22427/NTP-DATA-DTXSID001017359">https://doi.org/10.22427/NTP-DATA-DTXSID001017359</a> .

## Completed short-term NTP studies

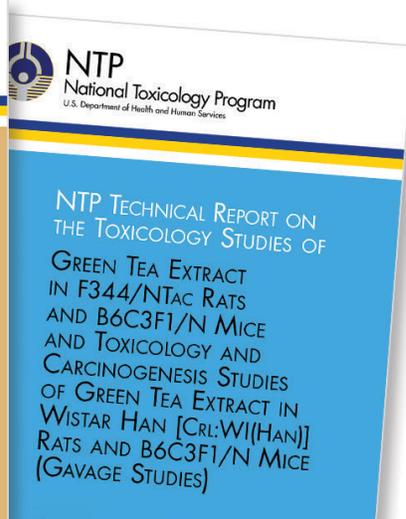
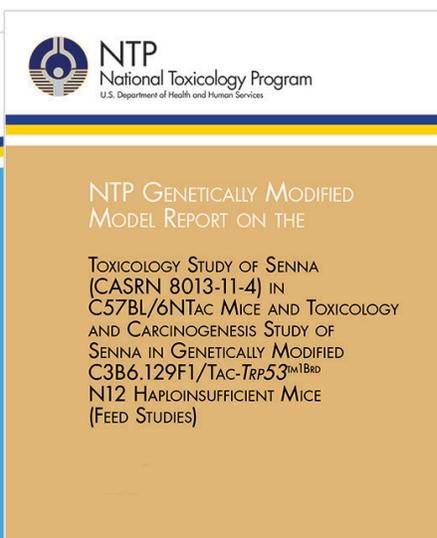
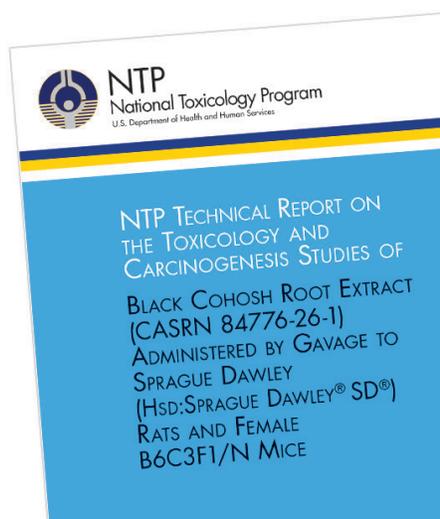
NTP studies are conducted in male and female rats and mice. Results from these studies may be analyzed with other data to assess the potential for cancer and other risks to human health.

Botanical Dietary Supplement	Rodent Study Results and Links to Select NTP Publications	Findings and Levels of Evidence of Carcinogenic Activity*
<b>Bitter Orange</b>	Hansen DK, George NI, White GE, Pellicore LS, Abdel-Rahman A, Fabricant D. 2012. Physiological effects following administration of Citrus aurantium for 28 days in rats. <i>Toxicol Appl Pharmacol</i> 261(3):236–247. <a href="http://www.ncbi.nlm.nih.gov/pubmed/22521485">www.ncbi.nlm.nih.gov/pubmed/22521485</a>	<b>Increased heart rate and blood pressure in female rats.</b>
	Hansen DK, Juliar BE, White GE, Pellicore LS. 2011. Developmental toxicity of Citrus aurantium in rats. <i>Birth Defects Res B Dev Reprod Toxicol</i> 92(3):216–223. <a href="http://www.ncbi.nlm.nih.gov/pubmed/21594979">www.ncbi.nlm.nih.gov/pubmed/21594979</a>	<b>No indication of developmental toxicity in rats.</b>
<b>Ephedra</b>	Nyska A, Murphy E, Foley JF, Collins BJ, Petranka J, Howden R, Hanlon P, Dunnick JK. 2005. Acute hemorrhagic myocardial necrosis and sudden death of rats exposed to a combination of ephedrine and caffeine. <i>Toxicol Sci</i> 83(2):388–396. <a href="http://www.ncbi.nlm.nih.gov/pubmed/15537744">www.ncbi.nlm.nih.gov/pubmed/15537744</a>	<b>Ephedra and caffeine caused damage to the heart muscle of male rats.</b>
	Dunnick JK, Kissling G, Gerken DK, Vallant MA, Nyska A. 2007. Cardiotoxicity of Ma Huang/caffeine or ephedrine/caffeine in a rodent model system. <i>Toxicol Pathol</i> 35(5): 657–664. <a href="http://www.ncbi.nlm.nih.gov/pubmed/17676524">www.ncbi.nlm.nih.gov/pubmed/17676524</a>	
<b>Gum Guggul</b>	NTP Report on Toxicity Studies of a Gum Guggul Extract Formulation Administered by Gavage to Sprague Dawley (Hsd: Sprague Dawley SD) Rats and B6C3F1/N Mice <a href="https://ntp.niehs.nih.gov/go/tox099">https://ntp.niehs.nih.gov/go/tox099</a>	<b>Decreased sperm count in male mice, decreased serum bile acid concentrations in female rats, increased serum cholesterol concentrations in female mice, and changes to metabolizing enzymes in male and female mice and rats.</b>
<b>Usnea Acid</b>	NTP Technical Report on the Toxicity Studies of (+)-Usnic Acid (CASRN 7562-61-0) Administered in Feed to F344/N Nctr Rats and B6C3F1/Nctr Mice. <a href="https://ntp.niehs.nih.gov/go/tox104">https://ntp.niehs.nih.gov/go/tox104</a>	<b>Caused liver damage and changes in estrous cycling in mice and rats, and genetic damage in mice.</b>
<b>Usnea Lichen</b>	NTP Technical Report on the Toxicity Studies of Usnea Lichens Containing (+/-)-Usnic acid (CASRN 125-46-2) Administered in Feed to F344/N Nctr Rats and B6C3F1/Nctr Mice. <a href="https://ntp.niehs.nih.gov/go/tox105">https://ntp.niehs.nih.gov/go/tox105</a>	



## Completed long-term NTP studies

Botanical Dietary Supplement	Rodent Study Results and Links to Select NTP Publications	Findings and Levels of Evidence of Carcinogenic Activity*			
		Male Rats	Female Rats	Male Mice	Female Mice
Aloe Vera	NTP Technical Report on the Toxicology and Carcinogenesis Studies of a Noncolorized Whole Leaf Extract of Aloe Barbadensis Miller (Aloe Vera) in F344/N Rats and B6c3f1 Mice (Drinking Water Studies) <a href="https://ntp.niehs.nih.gov/go/tr577">https://ntp.niehs.nih.gov/go/tr577</a>	Clear Evidence	Clear Evidence	No Evidence	No Evidence
	NTP Technical Report on the Photocarcinogenesis Study of Aloe Vera <a href="https://ntp.niehs.nih.gov/go/tr553">https://ntp.niehs.nih.gov/go/tr553</a>	Cancer of the large intestine in male and female rats, but not mice Weak cancer effect in mice with simulated sunlight on skin			
Black Cohosh	NTP Technical Report on the Toxicology and Carcinogenesis Studies of Black Cohosh Root Extract (CASRN 84776-26-1) Administered by Gavage to Sprague Dawley (Hsd:Sprague Dawley® SD®) Rats and Female B6C3F1/N Mice <a href="https://ntp.niehs.nih.gov/go/tr603">https://ntp.niehs.nih.gov/go/tr603</a>	Not Tested	Equivocal Evidence	Not Tested	No Evidence
		No evidence of causing cancer in male rats when mothers were exposed; decreased litter size in rats			
Ginkgo Biloba	NTP Technical Report on the Toxicology and Carcinogenesis Studies of Ginkgo Biloba Extract in F344/N Rats and B6C3F1/N Mice <a href="https://ntp.niehs.nih.gov/go/tr578">https://ntp.niehs.nih.gov/go/tr578</a>	Some Evidence	Some Evidence	Clear Evidence	Clear Evidence
		Cancer of the thyroid glands in male and female rats and male mice; cancer of liver in male and female mice			
Ginseng	NTP Technical Report on the Toxicology and Carcinogenesis Studies of Ginseng in F344/N Rats and B6C3F1 Mice <a href="https://ntp.niehs.nih.gov/go/tr567">https://ntp.niehs.nih.gov/go/tr567</a>	No Evidence	No Evidence	No Evidence	No Evidence
		No evidence of causing cancer in rats or mice			
Goldenseal	NTP Technical Report on the Toxicology and Carcinogenesis Studies of Goldenseal Root Powder in F344/N Rats and B6C3F1 Mice <a href="https://ntp.niehs.nih.gov/go/tr562">https://ntp.niehs.nih.gov/go/tr562</a>	Clear Evidence	Clear Evidence	Some Evidence	No Evidence
		Cancer of the liver in male and female rats and male mice, but not female mice			
Green Tea Extract	NTP Technical Report on the Toxicology Studies of Green Tea Extract in F344/NTac Rats and B6C3F1/N Mice and Toxicology and Carcinogenesis Studies of Green Tea Extract in Wistar Han[Crl:WI(Han)] Rats and B6C3F1/N Mice <a href="https://ntp.niehs.nih.gov/go/tr585">https://ntp.niehs.nih.gov/go/tr585</a>	No Evidence	No Evidence	No Evidence	No Evidence
		No evidence of causing cancer in rats or mice, but saw damage to the liver			
Kava or Kava Kava	NTP Technical Report on the Toxicology and Carcinogenesis Studies of Kava Kava Extract in F344/N Rats and B6C3F1 Mice <a href="https://ntp.niehs.nih.gov/go/tr571">https://ntp.niehs.nih.gov/go/tr571</a>	Equivocal Evidence	No Evidence	Clear Evidence	Clear Evidence
		Cancer of the liver in male and female mice, and some increases in tissue damage			
Milk Thistle	NTP Technical Report on the Toxicology and Carcinogenesis Studies of Milk Thistle Extract in F344/N Rats and B6C3F1 Mice <a href="https://ntp.niehs.nih.gov/go/tr565">https://ntp.niehs.nih.gov/go/tr565</a>	No Evidence	No Evidence	No Evidence	No Evidence
		No evidence of causing cancer in rats or mice			
Senna	NTP Report on the Toxicology Study of Senna in C57BL/6NTac Mice and Toxicology and Carcinogenesis Study of Senna in Genetically Modified C3B6.129F1/Tac-Trp53 <sup>tm1Brd</sup> N12 Haploinsufficient Mice <a href="https://ntp.niehs.nih.gov/go/gmm15">https://ntp.niehs.nih.gov/go/gmm15</a>	Not Tested	Not Tested	No Evidence	No Evidence
		No evidence of causing cancer in genetically modified mice; damage to large intestine			





## What are next steps for NTP's botanical dietary supplements program?

A public-private partnership, called the Botanical Safety Consortium, was formed by the FDA, the National Institute of Environmental Health Sciences (NIEHS), and the nonprofit Health and Environmental Sciences Institute (HESI) in November 2019. It provides an international forum in which scientists from government, academia, consumer health groups, industry, and nonprofit organizations can collaborate.

This consortium has already hosted a number of events as it works to create a sound scientific basis for integrating existing data and the latest toxicology tools to evaluate the safety of botanical dietary supplements. Learn more at [www.botanicalsafetyconsortium.org](http://www.botanicalsafetyconsortium.org).

## Botanical Dietary Supplements Where can I find more information?

### NIH National Center for Complementary and Integrative Health: Herbs at a Glance

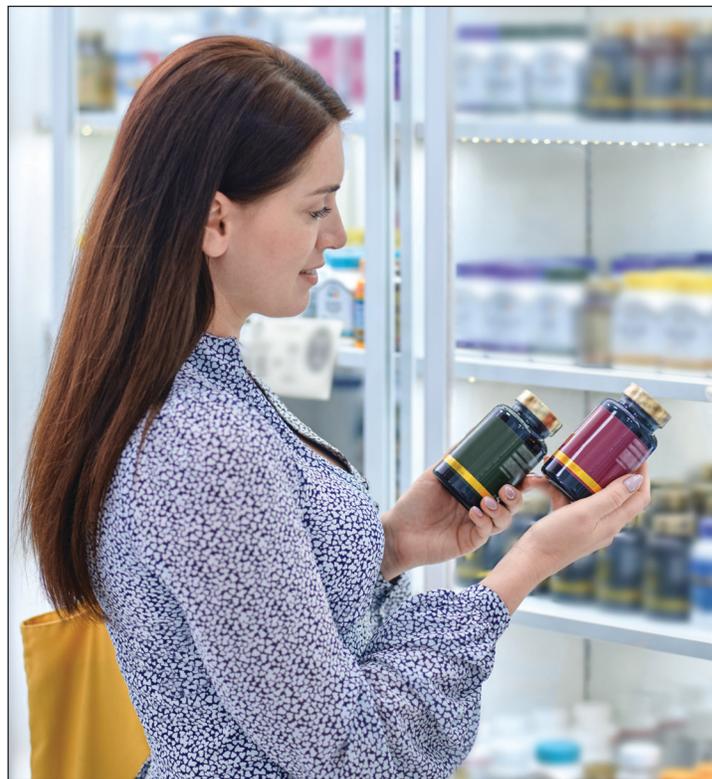
[www.nccih.nih.gov/health/herbsataglance.htm](http://www.nccih.nih.gov/health/herbsataglance.htm)

### NIH Office of Dietary Supplements: Botanical Supplement Fact Sheets

[www.ods.od.nih.gov/factsheets/list-botanicals](http://www.ods.od.nih.gov/factsheets/list-botanicals)

### U.S. Food and Drug Administration: Dietary Supplements

[www.fda.gov/food/dietarysupplements](http://www.fda.gov/food/dietarysupplements)



National Toxicology Program  
U.S. Department of Health and Human Services

Founded in 1978, NTP is an interagency program that includes NIEHS of the National Institutes of Health (NIH), the National Center for Toxicological Research of the FDA, and the National Institute for Occupational Safety and Health of the Centers for Disease Control and Prevention.

These agencies are all part of the U.S. Department of Health and Human Services (HHS).

For more information on the National Toxicology Program, go to <https://ntp.niehs.nih.gov>.



<sup>1</sup> Smith T, Resetar H, Morton C. US sales of herbal supplements increase by 9.7% in 2021. *HerbalGram*. 2022;136:42-69 [accessed December 16, 2022].

<sup>2</sup> FDA (U.S. Food and Drug Administration). 2019. Dietary Supplements. Available: [www.fda.gov/food/dietary-supplements](http://www.fda.gov/food/dietary-supplements) [accessed April 27, 2020].

<sup>3</sup> FDA (U.S. Food and Drug Administration). 2019. Statement on warning for women of childbearing age about possible safety risks of dietary supplements containing vinpocetine. Available: [www.fda.gov/news-events/press-announcements/statement-warning-women-childbearing-age-about-possible-safety-risks-dietary-supplements-containing](http://www.fda.gov/news-events/press-announcements/statement-warning-women-childbearing-age-about-possible-safety-risks-dietary-supplements-containing) [accessed July 13, 2020].

<sup>4</sup> NTP (National Toxicology Program). 2013. Toxicology and Carcinogenesis Studies of a Nondecolorized Whole Leaf Extract of Aloe Barbadosis Miller in F344/N Rats and B6C3F1 Mice (Drinking Water Study) Available: <https://ntp.niehs.nih.gov/publications/reports/tr/500s/tr577>

<sup>5</sup> Oketch-Rabah HA et al. 2020. United States Pharmacopeia (USP) comprehensive review of the hepatotoxicity of green tea extracts. *Tox Reports* 7:386-402.