



NTP Botanical Dietary Supplements Program

What are botanical dietary supplements?

Botanical dietary supplements are sometimes referred to as herbals or herbal dietary supplements. Botanical dietary supplements are available to consumers as plants, plant parts, or plant extracts. A dietary supplement is defined, in part, as a product intended for ingestion that may contain one or more dietary ingredients, and is intended to supplement the diet. Dietary supplements may be found in many forms, such as tablets, capsules, softgels, gelscaps, liquids, or powders. Some botanical dietary supplements are used in complementary and alternative medicine, also sometimes called traditional medicine.¹

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

NTP has received a number of nominations to study botanical dietary supplements from the public and other federal agencies, because people are concerned about the safety of these products.

Dietary supplements containing ingredients of botanical origin are widely available in the United States. A nationwide government survey found that natural products, including botanical dietary supplements, are frequently used by adults and children. Approximately 18 percent of adults, 18 years or older, and 4 percent of children use natural products, such as botanical dietary supplements.²

The U.S. Food and Drug Administration (FDA) is responsible for taking action against any unsafe dietary supplement, after it reaches the market.³ If a manufacturer wants to distribute a supplement containing a new dietary ingredient, they must notify the FDA prior to putting it on the market. However, notification does not mean that the FDA has determined that use of the new dietary ingredient is safe.⁴

For these reasons, NTP is conducting numerous studies in rodents to identify potential adverse effects of these agents after both short-term and long-term exposure.

NTP is conducting studies in rodent models to identify potential adverse effects of botanical dietary supplements.



These studies may provide toxicology data that can be used by the FDA, the National Institutes of Health (NIH), the public, and other stakeholders in evaluating the safety of supplements, and may lead to removal of unsafe products from the market.

How does NTP evaluate botanical dietary supplements?

Researching the potential adverse effects of botanical dietary supplements presents several unique challenges. For example, many supplements contain a complex mixture of ingredients, making it difficult to identify and link active ingredients to observed outcomes. Growing, harvesting, and processing conditions also can affect the chemical makeup of a botanical supplement. Possible contaminants in a botanical dietary supplement, such as metals, molds, and pesticides, may also affect its toxicity. For these reasons, NTP fully characterizes the chemical and physical composition of the botanical dietary supplements studied in its testing program.

NTP conducts toxicology studies in animal models under strict guidelines, to understand what happens once the supplement enters the body. NTP also conducts additional studies, including non-animal-based studies, to learn about the mechanisms of action.

These studies focus on characterizing potential adverse health effects, such as cancer. NTP looks at toxicity that results from short-term exposure to high doses, long-term exposure to lower doses, or a combination of both. NTP also examines toxicities to specific systems, including the reproductive, neurological, cardiovascular, and immune systems.





Completed NTP studies

NTP studies are conducted in male and female rats and mice. Multiple doses are given over two years, with doses that are typically higher than what humans are exposed to. These studies may be used in conjunction with other data to assess cancer and other adverse health risks to humans.

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 <i>Aloe Barbadensis</i> Miller (<i>Aloe Vera</i>) in F344/N Rats and B6c3f1 Mice (Drinking Water Studies) http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/TR577_508.pdf	Clear Evidence	Clear Evidence	No Evidence	No Evidence
	NTP Technical Report on the Photocarcinogenesis Study of <i>Aloe Vera</i> http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/TR553.pdf	Cancer of the large intestine in male and female rats, but not mice			
Ginkgo Biloba	NTP Technical Report on the Toxicology and Carcinogenesis Studies of <i>Ginkgo Biloba</i> Extract in F344/N Rats and B6C3F1/N Mice http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/TR578_508.pdf	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 http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/TR567.pdf	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 http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/TR562.pdf	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/N Rats and B6C3F1/N Mice and Toxicology and Carcinogenesis Studies of Green Tea Extract in Wistar Han[CrI:WI(Han)] Rats and B6C3F1/N Mice http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/TR585_508.pdf	No Evidence	No Evidence	No Evidence	No Evidence
		No evidence of causing cancer in rats or mice			
Kava or Kava Kava	NTP Technical Report on the Toxicology and Carcinogenesis Studies of Kava Kava Extract in F344/N Rats and B6C3F1 Mice http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/TR571.pdf	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 http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/TR565.pdf	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 <i>Senna</i> in C57BL/6NTac Mice and Toxicology and Carcinogenesis Study of <i>Senna</i> in Genetically Modified C3B6.129F1/Tac-Trp53 ^{tm1Brd} N12 Haploinsufficient Mice http://ntp.niehs.nih.gov/NTP/htdocs/gmm_rpts/gmm15_508.pdf	Not Tested	Not Tested	No Evidence	No Evidence
		No evidence of causing cancer in genetically modified mice, damage to large intestine			
Bitter Orange	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. http://www.ncbi.nlm.nih.gov/pubmed/22521485	Increased heart rate and blood pressure in female rats			
	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. http://www.ncbi.nlm.nih.gov/pubmed/21594979	No indication of developmental toxicity in rats			
Ephedra	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. http://www.ncbi.nlm.nih.gov/pubmed/15537744	Ephedra and caffeine caused damage to heart muscle of male rats			
	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. http://www.ncbi.nlm.nih.gov/pubmed/17676524				

*The NTP conclusions regarding levels of evidence of carcinogenic activity are based on a four-level scale: clear, some, equivocal, and no evidence.



Ongoing NTP studies

Botanical Dietary Supplements Currently Being Studied by NTP	
Black Cohosh	Member of the buttercup family. The perennial plant is native to North America. More information can be found at http://ntp.niehs.nih.gov/go/TS-M000058 .
Dong Quai	Plant that is native to China. More information can be found at http://ntp.niehs.nih.gov/go/TS-08032 .
Echinacea Purpurea	Plant that is native to the U.S. and southern Canada. It is used fresh or dried to make teas, juice, extracts, or other preparations. More information can be found at http://ntp.niehs.nih.gov/go/TS-M990067 .
Evening Primrose Oil	Comes from the plant evening primrose, which is native to North America, but also grows in other parts of the world. More information can be found at http://ntp.niehs.nih.gov/go/TS-09040 .
Garcinia Cambogia	Often grown for its fruit, which is used for cooking, food preservation, and as a dietary aid. More information can be found at http://ntp.niehs.nih.gov/go/TS-M050016 .
Gum Guggul	Resin of <i>Commiphora mukul</i> , a plant that is native to India. It is used in incense, ointments, and perfumes. More information can be found at http://ntp.niehs.nih.gov/go/TS-M050066 .
Usnea Lichen	A type of lichen that grows on trees all over the world. More information can be found at http://ntp.niehs.nih.gov/go/TS-09063 .
Valerian	A plant that is native to Asia and Europe, but is 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 http://ntp.niehs.nih.gov/go/TS-09042 .

What do NTP studies mean for humans?

NTP rodent studies on botanical dietary supplements represent an initial step in characterizing potential human health risks. Federal regulatory agencies may also bring together additional data to more fully understand the risks. Additional steps can include identifying the components in the botanicals that may account for adverse health effects, understanding how certain effects are caused, and determining how much and how often people consume or use these products.

Natural does not mean safe. Many supplements contain active ingredients that have strong biological effects that may interact with over-the-counter and prescription drugs. Safety is not always assured in all users. If you believe you have experienced an adverse event related to a dietary supplement, contact the FDA MedWatch program at <http://www.fda.gov/Safety/MedWatch>. This fact sheet is not intended to provide medical advice. Patients should have conversations with their doctors about starting or stopping the use of any supplement.





Botanical Dietary Supplements



Where can I find more information?

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

<http://nccih.nih.gov/health/herbsataglance.htm>

NIH Office of Dietary Supplements: Botanical Supplement Fact Sheets

<http://ods.od.nih.gov/factsheets/list-Botanicals>

U.S. Food and Drug Administration: Dietary Supplements

<http://www.fda.gov/Food/DietarySupplements>

NTP Fact Sheet on *Aloe Vera*

http://www.niehs.nih.gov/health/materials/aloe_vera_508.pdf

NTP Fact Sheet on *Ginkgo Biloba*

http://www.niehs.nih.gov/health/assets/docs_f_o/ntp_ginkgo_508.pdf



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

NTP is an interagency program involving the National Institute of Environmental Health Sciences (NIEHS), part of the National Institutes of Health (NIH), U.S. Food and Drug Administration (FDA), and the National Institute for Occupational Safety and Health (NIOSH) of the Centers for Disease Control and Prevention (CDC). NTP is headquartered at NIEHS.

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



¹ NCCIH (National Center for Complementary and Integrative Health). 2016. Complementary, Alternative, or Integrative Health: What's In a Name? Available: <http://nccih.nih.gov/health/integrative-health> [accessed April 7, 2016].

² Barnes PM, Bloom B, Nahin RL. 2008. Complementary and alternative medicine use among adults and children: United States, 2007. National Health Statistics Report No. 12. Hyattsville, MD: National Center for Health Statistics.

³ NIH/ODS (National Institutes of Health Office of Dietary Supplements). 1994. Dietary Supplement Health and Education Act of 1994, Public Law 103-417, 103rd Congress. Available: http://ods.od.nih.gov/About/DSHEA_Wording.aspx [accessed April 7, 2016].

⁴ FDA (U.S. Food and Drug Administration). 2014. New Dietary Ingredients in Dietary Supplements – Background for Industry. Available: <http://www.fda.gov/Food/DietarySupplements/NewDietaryIngredientsNotificationProcess/ucm109764.htm> [accessed April 7, 2016].