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American Herbal Products Association's

BOTANICAL SAFETY HANDBOOK

Second Edition

Edited by
Zoë Gardner
Michael McGuffin

Expert Advisory Council
Roy Upton
Soaring Bear
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AMERICAN HERBAL PRODUCTS ASSOCIATION

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DEDICATION

This book is dedicated to the memory of Mary Frances Picciano, Ph.D., former Senior Nutrition Research Scientist at the Office of Dietary Supplements, National Institutes of Health. Her interest, foresight, and willingness to have the Office of Dietary Supplements support a partnership with the American Herbal Products Association and the University of Massachusetts made this work possible.

CONTENTS

PREFACE TO THE FIRST EDITION

Increased attention on herbal products, both in the marketplace and in the legislative arena, has created a need for wider public access to data regarding the safety of botanicals. The passage of the Dietary Supplement Health and Education Act in October, 1994, furthered the need for such information, as this law authorizes the use of cautionary labeling for dietary supplements, including those that contain herbs.

The American Herbal Products Association (AHPA), through its Standards Committee, convened a special SubCommittee (hereinafter "the Committee") to address this need. The Committee members identified considerable safety data in varied texts and journals and discovered that some attempts to classify herbs had been undertaken in several other countries. No comprehensive compilation or review of this data for botanical ingredients sold in the North American marketplace, however, was available in a useful format.

The goal of the present work is to find a rational platform for the evaluation of herb safety, neither assuming that all natural substances are inherently safe, as some popular references suggest, nor blindly accepting reports of toxicity from uncritical sources. In undertaking this task, the Editors met with information that presented significant challenges. Many authors utilize unreferenced data, perpetuate historical inaccuracies or display inherent biases against the use of botanicals. Also, contemporary reviews of the toxicity of many herbs are not available. Nonetheless, the Editors are confident that the body of information presented here is largely accurate. It is our sincere hope that readers of this work will find it to be a valuable reference and will address all useful criticisms to our attention.

In sponsoring this effort, the American Herbal Products Association (AHPA) addresses the common interest of industry, the public, and regulatory agencies in assuring safe access to a wide range of herbs and herbal products. This document provides accurate data to guide manufacturers and consumers in safe utilization of herbal products. As the most broadly established trade association in the herbal marketplace, AHPA has, by supporting and sponsoring the creation of this work, furthered the herb industry's leadership role in promoting the responsible use of herbs.

PREFACE

This second edition of AHPA's *Botanical Safety Handbook* represents a significant modification from the first edition, published in 1997. At the same time, the second edition reflects the continued commitment of the American Herbal Products Association (AHPA) to provide accurate information about the safe use of herbs in a practical and accessible format.

The original edition classified botanical ingredients in four safety classifications to differentiate those that can be safely consumed when used appropriately from those for which some contraindication or other restriction is known, as well as those that should be used only under the guidance of a qualified expert. A handful of entries in that edition were also placed in a separate class if the editors had insufficient data for classification. The revised edition largely retains this safety classification system, except that if the review process did not provide enough information to make a knowledgeable decision on any specific herb, that species was removed from the text.

The present edition also includes a separate classification system to address what is known about the potential for an herb to interact with any drugs. Each of the herbs listed here is identified in one of three interaction classes to differentiate between those for which no clinically relevant interactions are expected and those for which clinically relevant interactions are biologically plausible or are, in fact, known to occur.

Botanical products continue to be broadly used throughout the world. In the United States, most herbs are sold in loose form or as tablets, capsules, or tinctures, and regulated as dietary supplements (this product class also includes vitamins, minerals, amino acids, and numerous other ingredients). Many herbs are also common flavorings for foods, or are used in teas. In addition, a handful of herbs provide active ingredients in non-prescription drugs. The U.S. marketplace for herbal products in the supplement category has increased significantly in the years since publication of the first edition, and the retail value of this product category grew from $3 billion in 1996 (Muth et al. 1999) to $5 billion in 2010 (Anon. 2011).

An even more significant change in the past 15 years has been the emergence of the Internet and online scientific databases as tools for accessing scientific information. The first edition of this book relied almost entirely on secondary references (i.e., books and other summaries of traditional or scientific information), and the editors of that document used their personal collections of such texts to compile the information needed to make safety determinations for the plants addressed in it. On the other hand, the process for compiling information for this second edition, as described in the introduction, involved a much more thorough review of primary references (i.e., published research papers, case reports, and other original literature). Thus, while the first edition included just 280 references to evaluate the over 500 plants addressed therein, this revision cites 301 references just in its treatment of St. John's wort herb (*Hypericum perforatum*), ginkgo leaf and seed (*Ginkgo biloba*), and garlic bulb (*Allium sativum*).

Any attempt to provide a summary of safety information on botanicals will encounter certain prejudices and inaccuracies in the published record. One such prejudice, often repeated in reviews of herbal medicines and dietary supplements, is the view that consumers have been led to believe the myth that "anything natural is safe" (Barnes 2003; Dasgupta and Bernard 2006). While one survey of consumer attitudes in Canada found that 7 percent of respondents completely agree that there is no risk associated with products made with natural ingredients (Anon. 2005), there are no published analyses of consumer beliefs that indicate that there is broad acceptance of any such assumption.

It is, however, true that many of the plants that enjoy broad culinary and traditional therapeutic usage are generally safe. We can safely season our food with any number of herbs to make a meal more flavorful. We can appreciate a delicious cup of peppermint leaf or rose hips tea, or safely take an herbal supplement containing dandelion root, saw palmetto berries, or any number of other herbs. Although allergies and individual reactions have been recorded for a few herbs that are widely used in foods and supplements, such individual concerns are also seen with many other foods, and do not diminish the safety profile of the many herbs that are widely regarded as safe.

On the other hand, and as everyone knows, there are any number of plants that are highly toxic, even deadly. Every savvy North American hiker knows to stay away from poison ivy (*Toxicodendron* spp.) when walking in the woods. The death sentence imposed on Socrates by an Athenian jury 2,400 years ago was carried out with a fatal dose of poison hemlock (*Conium maculatum*). The poison curare, a blend of several equatorial rain forest plants (e.g., species of *Chondrodendron*, *Curarea* and *Strychnos*) is used by some South American hunter cultures to make their arrows more deadly (Schultes and Raffauf 1990). And in

the "concrete jungle" of Los Angeles, two young boys died in 2000 from ingesting a few leaves of the ubiquitous oleander (*Nerium oleander*) (Garrison 2000). Federal law and good common sense, however, prevent the use of any such highly toxic plants in products that are readily available to consumers.

The revised edition of the *American Herbal Products Association's Botanical Safety Handbook* fills the need for a reference that neither promulgates the myth that all herbs are always safe, since they are "natural," nor accepts without review every case report or conceptual theory that draws an unsubstantiated or illogical conclusion of harm from an herb or herbal product. In assembling this revision, significant effort has gone into sorting out references that are factual from those that are inaccurate. Texts that communicate that all natural substances are inherently safe would not have been included here, though in fact no such documents were encountered. More effort was needed to avoid blind acceptance of reports that purport to identify herbal safety concerns with unreferenced statements or incomplete records of specific herbal preparations, which are unfortunately quite common, even in peer-reviewed scientific journals. Such references may nonetheless be included in this text to provide readers with a complete record, though efforts were made to highlight any perceived flaws.

Even as the consumer market for herbal supplement products expands and scientific information becomes more accessible, the goals of the second edition of the AHPA's *Botanical Safety Handbook* are essentially the same as those of the original edition. Companies that market herbal products are bound by federal regulations to disclose known safety concerns that may result from a product's use. Health care providers, especially those lacking in training or experience in the use of herbs, are in need of accurate data if they are to provide guidance to their patients who use herbs. And consumers of herbs and herbal products need readily understandable information to assist them in making safe and appropriate health care choices. AHPA's *Botanical Safety Handbook, 2nd edition* is designed to provide the information needed by each of these audiences.

It should be recognized, however, that this reference is not an herbal user's guide. Numerous excellent references exist that provide information on the uses and benefits of herbs. Readers of the present document are advised to seek out these references, or to consult with experts qualified by training and experience, for advice on when and how to use herbs for their health benefits.

The editors are confident that the body of information presented in this second edition of the AHPA *Botanical Safety Handbook* is largely accurate, and hope that readers of this work will find it to be a valuable reference. Useful criticisms will nonetheless be welcome, and should be addressed to the attention of the editors.

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The members of this edition's Expert Advisory Council met together on a regular basis for nearly five years, all on their own time, and without any financial compensation. The expertise and experience embodied in these individuals are unsurpassed, and without them the work could not have proceeded beyond a collection of references, as it was through their efforts that these references were evaluated and organized into the present text. Biographies of each of these individuals follow.

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Thanks are also due to the generations of herbalists and scientists around the world whose research and experience have provided the basis for our understanding of the safety of medicinal plants. Their work and publications have created a significant foundation for our understanding of the safety of the botanicals reviewed in the present text.

Appreciation is also due to Joseph Betz, Ph.D. and the late Mary Frances Picciano, Ph.D. of the Office of Dietary Supplements (ODS) at the National Institutes of Health. Dr. Betz shared his ideas on the makeup of the Expert Advisory Council and on the importance of addressing the potential for an herb to modify the effect of a drug taken concomitantly, commonly referred to as an herb–drug interaction (a topic that was outside of the scope of the first edition). Dr. Picciano facilitated ODS's significant financial support of the revision process and ensured that the planned revision met high academic and scientific standards.

A number of research assistants helped to acquire and manage the thousands of documents reviewed in this project. A work of this scope would not have been possible without the enthusiastic assistance of Jamie Blair, Brittney Laramee, Annie Winkler, Ryan Rogan, Rye Zemelsky, Kathleen Broadhurst, Jennifer Kehoe, Margo Voskanian, Jennifer Hast, and Abigail Haines. Thanks are also due to Constance Parks and Bill Schoenbart for their detailed reading and editing of the manuscript.

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Fascinated by the connection between people and plants, Zoë Gardner has been studying, researching, and teaching on the production, conservation, quality, safety, and appropriate use of medicinal plants since 1998. After completing her undergraduate degree in environmental studies at the Audubon Expedition Institute, Zoë helped to establish the Medicinal Plant Program at the University of Massachusetts, earning her master's degree there in plant & soil sciences. More recently, Zoë joined the Research & Development Department at Traditional Medicinals, a leading producer of botanical dietary supplements. A self-proclaimed "herb nerd," Zoë is currently completing her Ph.D. on medicinal plant quality and safety.

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Michael McGuffin has been active in the herbal industry since 1975, having owned and managed both retail and manufacturing businesses in this field. He is the managing editor of *Botanical Safety Handbook, 1st edition* (1997) and of *Herbs of Commerce, 2nd edition* (2000). He serves on the boards of the American Herbal Pharmacopoeia and United Plant Savers; on the Advisory Board of the USC School of Pharmacy Regulatory Science Program; and as chair of the U.S. Technical Advisory Group for ISO/TC 249, the International Organization for Standardization's Technical Committee on Traditional Chinese Medicine (provisional title). Michael maintains active involvement with regulatory agencies, and served on FDA's Food Advisory Committee Working Group on Good Manufacturing Practices for Dietary Supplements (1998–1999), FDA's Food Advisory Committee's Dietary Supplements Subcommittee (2003–2005), and California's Office of Environmental Health Hazard Analysis Food Warning Workgroup (2008–2010).

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Roy Upton has been trained in traditional Ayurvedic, Chinese and Western herbal traditions, has studied Native American and Caribbean ethnobotanical traditions, and is a professional member of the American Herbalists Guild. He is the executive director and editor of the *American Herbal Pharmacopoeia* and a member of the Standards Committee of the American Herbal Products Association and advisory committees for the American Botanical Council, AOAC International, and NSF International. Along with being an author and lecturer, Roy was co-founder and past president of the American Herbalists Guild and is the herbalist and director of the California-based herbal company Planetary Herbals.

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David Winston is an herbalist and ethnobotanist with over 40 years of training in Cherokee, Chinese, and Western/Eclectic herbal traditions. David is a founding/professional member of the American Herbalists Guild and has been in clinical practice for over 33 years. He is an herbal consultant to many physicians and other healthcare professionals throughout the U.S. and Canada. David is also the president of Herbalist & Alchemist, Inc. and founder and director of David Winston's Center for Herbal Studies and the Herbal Therapeutics Research Library. He is the author of numerous texts on herbal medicine, is an internationally known lecturer, and teaches frequently at medical schools, symposia, and herb conferences.

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Daniel Gagnon, owner of Herbs, Etc., has been a practicing herbalist since 1976. Daniel has studied medical herbalism, pharmacognosy, and related subjects at the Santa Fe College of Natural Medicine, the College of Santa Fe, and the University of New Mexico. He received his B.S. in herbal medicine from the North American College of Botanical Medicine and his M.S. in herbal medicine from the Scottish School of Herbal Medicine. Daniel was a faculty member of the North American College of Botanical Medicine for over 10 years and currently serves as an herbal consultant to healthcare providers. He is the author of several books on herbal medicine.

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Before becoming a physician, Dr. Aviva Romm was a recognized expert in midwifery, women's health, and women's and pediatric botanical medicine, and she practiced as a homebirth midwife and herbalist for over 20 years. A graduate of the Yale School of Medicine, she completed her internship in internal medicine (Yale) and her residency in family medicine (Tufts). She was the president of the American Herbalists Guild, the founder and director of Herbal Medicine for Women, a distance learning program, and is the medical director for the American Herbal Pharmacopoeia. Dr. Romm has been active in establishing standards for botanical medicine practice and education in the United States, and is the author of numerous texts on botanical medicine, pregnancy, and children's health.

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Dr. Tieraona Low Dog's extensive career in natural medicine began more than 25 years ago. A graduate of the University of New Mexico School of Medicine, Tieraona has served as president of the American Herbalists Guild and is currently the Director of the Fellowship at the Arizona Center for Integrative Medicine at the University of Arizona School of Medicine. She has been involved in national health policy and regulatory issues, serving previously on the White House Commission of Complementary and Alternative Medicine and as a member of the Advisory Council for the National Center for Complementary and Alternative Medicine, and is currently chair of the U.S. Pharmacopeia Dietary Supplements and Botanicals Expert Committee.

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Dr. Mary Hardy is an integrative medicine physician who received her Doctor of Medicine degree from Louisiana State University School of Medicine and studied medical ethics at Harvard Divinity School and Loma Linda University. She has studied with herbal practitioners in the United States and Europe and visited traditional healers in Peru, Kenya, South Africa, Morocco and China. She is the complementary and alternative medicine expert for a number of research projects conducted by the Southern California Evidence-Based Practice Center at the RAND Corporation, co-chairperson of the Clinical Practice Committee of the Academic Consortium of Integrative Medicine, and associate director of the UCLA Botanical Research Center, funded by the National Institutes of Health.

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Dr. Lyle Craker has been a researcher in the field of medicinal plants for over 30 years. With a Ph.D. in agronomy from the University of Minnesota, he is founding and past editor of the *Journal of Herbs, Spices, and Medicinal Plants*, founding and current executive editor of the *Journal of Medicinally Active Plants*, past chairman of the International Society for Horticultural Science (ISHS) Section on Medicinal and Aromatic Plants, organizer of the Herb, Spice, & Medicinal Plant Working Group within the American Society for Horticultural Science (ASHS), and an organizing member of the International Council on Medicinal and Aromatic Plants and the American Council for Medicinally Active Plants. He is an advisory board member of the American Botanical Council and serves on the board of the AHPA Foundation for Education and Research on Botanicals.

INTRODUCTION

The second edition of AHPA's *Botanical Safety Handbook* provides information on a number of safety factors that may affect an individual's decision to ingest any of the herbal* substances listed in this work. The information was prepared through a process that involved identification of relevant publications on each botanical, as well as a review by experts qualified by training and experience in the traditional and therapeutic use of herbs and herbal products.

Each of the botanical ingredients† included in this text is classified into one or more Safety Class, and also into an Interaction Class, details of which are described below. These classifications, as well as a synopsis of pertinent information from reviewed references, are presented in a Quick Reference Summary, which provides basic data needed to understand safety issues associated with each botanical. This summary is followed by a section titled Review Details in which more in-depth information is presented when available. Thorough descriptions of the templates and contents of each of these sections are provided later in this introduction.

DETERMINATION OF HERB SAFETY

In developing this document, the voices and experience of various organizations and individuals were considered. A primary source of guidance and inspiration for the first edition of this text was the work of the World Health Organization (WHO). In 1991, WHO's Programme on Traditional Medicines presented Guidelines for the Assessment of Herbal Medicines at the Sixth International Conference of Drug Regulatory Authorities. These guidelines, which were subsequently reviewed and adopted by WHO, propose that the safety of herbal medicine be assessed according to the following principle:

> *…that if the product has been traditionally used without demonstrated harm, no specific restrictive regulatory action should be undertaken unless new evidence demands a revised risk-benefit assessment. (WHO 1991)*

The editors of the first edition adopted this principle from the WHO Guidelines and this view has been maintained for the compilation of the present work.

In his classic text, *The Problem of Poisonous Plants*, J.M. Kingsbury provides further direction by calling attention to the fact that there are many instances in which a plant contains a measurable amount of a toxic substance, though the plant may be poisonous only if consumed in excessive quantities. He notes:

> *In order for a plant to be functionally poisonous, it must not only contain a toxic secondary compound, but also possess effective means of presenting that compound to an animal in sufficient concentrations, and the compound must be capable of overcoming whatever physiological or biochemical defenses the animal may possess against it. Thus the presence of a known poison principle, even in toxicologically significant amounts, in a plant does not automatically mean that either man or a given species of animal will ever be effectively poisoned by the plant. (Kingsbury 1979)*

In examining the relevance of Kingsbury's position, it is of interest to revisit the means by which concerns for the safety of herbs arise. Toxicity studies are often conducted by feeding abnormally high quantities of an herb or isolated constituent of an herb to laboratory animals. For example, Bensky and Gamble report in their monograph on mulberry leaves that "long-term use of 250 times the normal human dose in mice produced both liver and kidney damage" (Bensky and Gamble 1986). Data based on excessive consumption have little relevance to the practical use of herbal supplements, and such findings are clearly not pertinent to normal human consumption patterns. In addition, information is sometimes available that identifies an LD_{50} for an herb, herbal preparation, or isolated compound (i.e., the "lethal dose" at which 50 percent of test animals are killed by the studied substance), but often fails to specify the concentration or form of the specific material used. Such incomplete data cannot be accurately applied to safety evaluations of human consumption.

Significant toxicity data exist for isolated constituents of a wide variety of commonly available foods, as well as herbs. Potatoes, as a member of the Solanaceae family, contain trace amounts of the toxic glycoalkaloid solanine, especially in green parts of the potato tuber (Turner and Szczawinski 1991). Although the symptoms of solanine poisoning are serious, potatoes themselves are generally considered to be a safe food. While consumption of

* The terms "herbal" and "botanical" are used interchangeably throughout this work.

† Or occasionally, groups of ingredients. Examples are listings for more than one plant part from a specific taxa, when the safety concerns for these are not different, or groups of two or more species within a genus, when these have common safety profiles.

as little as five grams of nutmeg can cause marked hallucinations (Sangalli and Chiang 2000), no safety concerns prevent us from enjoying a sprinkle of this characteristic flavor on our holiday eggnog. Similarly, no safety concern is associated with a candy flavored with peppermint oil, though as many as 26 toxins are reported to have been observed in the plant (Duke 1989). Safety concerns for herbal products need not be extrapolated from constituent profiles with any more alarm than is appropriate for foods.

In following the principles espoused by WHO and incorporating the ideas delineated by Kingsbury, it is imperative that herb safety be assessed according to the intended use of the substance within the historical context of its use. In establishing safety classifications, this work has intentionally refrained from automatically applying information on the toxicity of isolated constituents or considering excessive or irresponsible consumption patterns. The decision to place an herb in a restrictive safety class was made only if the use of the herb in a normal dosage range is documented as presenting a safety concern, or if the amount of a harmful or potentially harmful constituent obtainable from the crude plant is of sufficient quantity to be problematic.

ADDRESSING POTENTIAL DRUG INTERACTIONS

The issue of herb–drug interactions was specifically excluded from the first edition of this work, since at that time very little accurate information had been developed on this subject. In the years since then, this topic has been much more prominently studied. Some early publications on the subject were largely speculative, but researchers have now begun to develop scientifically based data that have measured actual effects of several herbs on the metabolism of selected drugs or on drug-metabolizing enzymes. At the same time, emerging research on many specific botanicals has confirmed that no drug interactions should be expected with these herbs.

Drug interactions are generally divided into two categories: pharmacodynamic interactions, in which the physiological effects of drugs or botanicals interact (including additive and opposing effects), and pharmacokinetic interactions, in which an interaction affects a drug's absorption, metabolism, or excretion, and changes the amount and duration of a drug's bioavailability (see CYP450 and P-gp interactions profile in Appendix 3). While pharmacodynamic interactions are generally predictable based on the pharmacological effects of drugs and botanicals, pharmacokinetic interactions, until identified through testing or well-documented case reports, generally cannot be predicted.

This work focuses primarily on pharmacokinetic interactions, although a small number of pharmacodynamic interactions are also listed, especially when such interactions may have significant health consequences (e.g., additive effects on heart medications or antiplatelet drugs). In pharmacokinetic herb–drug interactions, the severity of an interaction is generally based on the toxicity of the drug being used or the consequences if the therapeutic dose is not achieved. When herbs are used with drugs that have a narrow therapeutic window (i.e., small difference between the effective dose and the toxic dose, such as with digoxin, warfarin, lithium, cyclosporine, phenytoin, and theophylline), supervision by a qualified healthcare practitioner is strongly advised.

Both pharmacodynamic and pharmacokinetic interactions may have positive effects, such as increasing the efficacy or bioavailability of drugs or botanicals. Such positive therapeutic interactions are not covered in this text, unless the interaction also poses a safety concern.

SELECTION OF THE EXPERT ADVISORY COUNCIL

Methods and considerations for safety evaluations that are outlined in the U.S. Institute of Medicine's (IOM) *Framework for Evaluating the Safety of Dietary Supplements* provided guidance in the literature collection and review processes that went into the creation of this text (IOM 2005). This IOM document also highlights the importance of using experts from a number of fields related to dietary supplements. Consistent with this advice, an advisory panel of qualified experts was assembled at the outset of this project. All members were selected for their extensive knowledge and experience in areas such as medicine, clinical herbalism, pharmacology, biochemistry, or traditional herbal medicine systems (e.g., traditional Chinese medicine or Ayurvedic medicine). When knowledge of a particular topic or botanical was not found in the Expert Advisory Council, the experience and opinions of outside experts were solicited.

LITERATURE REVIEW METHODS

Systematic literature searches were conducted in several electronic databases from January 2007 to May 2010, using search terms developed in cooperation with a technical information specialist from the National Library of Medicine, as follows:

- PubMed ([Latin name] OR [standardized common name]) AND (adverse effects OR adverse reaction OR safety OR tolerability OR drug interactions OR herb–drug interactions OR poisoning OR toxic OR toxicity OR toxicology OR drug toxicity OR teratogen* OR contraindicat* OR cytochrome OR p450 OR pregnancy OR lactation OR breast feeding OR breast milk OR pharmacodynamics OR "[MeSH term]/adverse effects" OR "[MeSH term]/toxicity" OR (Case Reports[ptyp]))
- EMBASE and Biological Abstracts ([Latin name] OR [standardized common name]) AND (adverse drug reaction OR safety OR tolerability OR drug tolerability OR herb drug interaction OR drug interaction OR drug contraindication AND contraindication OR poisoning OR intoxication OR drug toxicity OR toxic OR toxicity OR toxicology OR teratogen OR teratogenic OR teratogenicity OR cytochrome OR pregnancy OR lactation)
- TOXNET ([Latin name] OR [standardized common name]) AND (teratogen* OR adverse effects OR safety OR tolerability OR drug interactions OR poisoning OR toxicity OR cytochrome OR contraindications OR pregnancy OR lactation) NOT PubMed

Literature selected from these searches for review included meta-analyses, systematic reviews, other reviews, clinical trials, human, animal and *in vitro* pharmacological studies related to safety (including drug interaction studies), toxicity studies including reproductive and developmental toxicity studies, epidemiological studies, and ethnobotanical surveys. Articles on combination products and homeopathic products were generally excluded. No language restrictions were imposed, so publications in other languages were included whenever possible, but the review focused on English language publications.

Besides this extensive literature review, numerous other publications were consulted. These consisted primarily of authoritative references on the traditional use of herbal medicines, and also included regulatory documents, ethnobotanical records, pharmacopoeial texts, and writings on toxicology, food ingredients, and other relevant topics.

Literature was identified, obtained, and summarized by the research editor. Full literature summaries were presented to the Expert Advisory Council and other experts as needed, for review and assignment of safety and interaction ratings, contraindications, and precautions. Ratings were assigned by the Expert Advisory Council bearing in mind the history of use of the botanical under review.

No formal assessment of the validity of each reference was undertaken in this process, although the levels of evidence afforded by different types of publications (i.e., case report vs. randomized, placebo-controlled double-blind study) were actively considered during the review process. In addition, it was observed that some identified publications were of limited value, especially those that lack sufficient detail about the specific herbal preparation addressed, and case reports that postulate a causal relationship between a specific herbal ingredient and a reported adverse effect, without consideration for confounding factors such as patient history or concomitant drug use. Some such references were nonetheless retained, though the editors attempted to call attention to their perceived flaws.

Additional articles in scientific journals that were published subsequent to the 2007 to 2010 review were also considered for several entries during the editing stages that followed the process described above.

THE REVIEW PROCESS AND CLASSIFICATION

The herbal ingredients included in this edition are very nearly the same as those included the first edition, published in 1997. Some other herbs were added in order to include ingredients that have become more prominent in the U.S. marketplace in the interim. A few herbs addressed in the first edition are not included here, usually because no relevant contemporary publications were found and evidence from historical sources was lacking or insufficient.

Classifications are included for each part of the plant* identified in an entry, and are for dried plant material, unless otherwise stated. Classifications address only the identified part of the herb in its whole, cut, or powdered form, as a raw material or as an ingredient in a finished product (tablets, capsules, teas, etc.); or as a decoction, tincture, or extract prepared from that plant part by a traditional process. Concentrated extracts, extracts with added compounds, or compounds isolated from botanicals may be expected to have different physiological effects and safety and interaction considerations than the source

* Plant parts identified as "herb" consist of the leaf and stem of the identified plant, and this term is generally used only for nonwoody plants. A plant part identified as "above-ground parts" means all of the plant above the ground, so it generally includes not only leaf and stem, but also flowers, fruits, and seeds, depending on the state of maturity of the plant at the time of harvest. All other plant parts (e.g., bark, leaf, root) are each identified with the generally used botanical term.

botanical, and classifications should not be extrapolated to other such ingredients without additional review.

Classifications are generally based on data that are associated with use of the specific herb and in the quantities generally consumed for a health-promoting or therapeutic effect. Any cautions may therefore be somewhat overstated for an herb that appears in the market in a smaller amount as part of a combination product, or for herbs that are used as flavorings in less than therapeutic quantities.

Each herb is placed in two classes based on all of the information included, along with the experience of the Expert Advisory Council. The first is the **Safety Class**, which evaluates the safety of a particular herb. The second is the **Interaction Class**, which provides information on what is currently known about the potential for an herb to alter the effect of prescription or non-prescription drugs when the herb and drug are used concomitantly. Central to the appropriate application of this document is the understanding that classifications are based on an assumption of rational, informed use of herbs and herbal products.

Classes are defined below, and are followed by bullet points which list criteria and considerations for inclusion in each particular class.

SAFETY CLASSES

Class 1. Herbs that can be safely consumed when used appropriately.

- History of safe traditional use
- No case reports of significant adverse events with high probability of causality
- No significant adverse events in clinical trials
- No identified concerns for use during pregnancy or lactation
- No innately toxic constituents
- Toxicity associated with excessive use is not a basis for exclusion from this class
- Minor or self-limiting side effects are not bases for exclusion from this class

Class 2.[*] Herbs for which the following use restrictions apply, unless otherwise directed by an expert qualified in the use of the described substance:

2a: For external use only

- Toxicity demonstrated with crude preparation taken orally at traditional dose
- Adverse event data in humans with probability of causality of toxicity (e.g., hepatotoxicity, nephrotoxicity, neurotoxicity) associated with oral use

2b: Not to be used during pregnancy

- Traditional use contraindicates
- Traditional use as an abortifacient or uterine stimulant
- Relevant adverse event data in humans exist and have probability of causality
- Data in animals suggesting teratogenicity or other adverse effects on the fetus or mother, with reasonable application to humans
- For plants with common food uses, standard dose is in excess of typical food amounts

2c: Not to be used while nursing

- Traditional use contraindicates
- Relevant adverse event data in humans exists and has probability of causality
- Potential hepatotoxicity or neurotoxicity
- Bioavailability of constituents of concern in breast milk has been demonstrated

2d: Other specific use restrictions as noted

- Information exists that use may be unsafe for specific populations
- Dosage level outside of a standard range known to cause adverse effects

Class 3. Herbs to be used only under the supervision of a qualified expert. The following labeling is recommended for Class 3 herbs: "To be used only under the supervision of an expert qualified in the appropriate use of this substance." Labeling must include proper use information: dosage, contraindications, potential adverse effects and drug interactions, and any other relevant information related to the safe use of the substance.

- Narrow therapeutic range
- Identified safety concerns in many populations

Interaction classes

Class A. Herbs for which no clinically relevant interactions are expected

- No case reports of suspected interactions with probability of causality
- No clinically relevant interactions in human pharmacological studies, if any

Class B. Herbs for which clinically relevant interactions are biologically plausible

- Human or animal pharmacological study data suggest potential for clinically relevant interaction.

[*] Herbs placed in any of the subparts of Class 2 may also be placed in other of these subparts.

- Multiple case reports have suggested a potential interaction concern.
- Cell culture or biochemical assays establish a basis for biologically plausible mechanism of interaction.

Class C. Herbs for which clinically relevant interactions are known to occur

- Human pharmacological study has demonstrated interaction with a specific drug or supplement.
- Human pharmacological study has demonstrated clinically relevant effects on drug metabolizing enzymes or drug transporter proteins.
- Case reports of suspected interactions have a probability of causality.

Limitations of Scope

This work specifically excludes the following data, conditions, and related products:

- Excessive consumption. Safety and interaction classifications given here are for normally consumed amounts, and cannot be assumed to have relevance for any quantity. Also, any concerns that are significant only in excessive or immoderate use are not relevant to assignation of classifications, though these may be referred to in an Editors' Note.
- Safety or toxicity concerns based on isolated constituents. As is the case with many common foods, some herbs are known to contain constituents that, in isolation, exhibit toxicity. Data based solely on constituents are not considered relevant to safety classification except in those cases where such compounds are known to accumulate, or where consumption patterns are sufficient to provide cause for health concerns. The presence of a constituent has been identified in a Notice if knowledge of the constituent is relevant to the safe use of an herb.
- Toxicity data based solely upon intravenous or intraperitoneal administration. The majority of herbal products consumed by the public are taken orally and with adequate dosage instructions. The physiological effects of injectable preparations are not relevant to oral consumption. Information associated with other forms of administration was reviewed but was not considered as a sole basis for classifications, and classifications should be assumed to address oral administration, unless otherwise stated.
- Traditional Chinese and Ayurvedic contraindications. In Chinese and Ayurvedic therapeutic traditions, most herbs have contraindications based on an individual's constitutional strengths and weaknesses, seasons, climate, and other factors that can only be understood in the context of the specific tradition. These traditional concerns have not been included in the text unless they can also be interpreted in a modern biomedical context, such as contraindication in pregnancy.
- Gastrointestinal disturbances. Reports of nausea or emesis from excessive doses, or occasional and/or minor gastrointestinal disturbances, have been noted but have not been considered in establishing safety classification, unless frequency or severity of such reactions warrants consideration.
- Idiosyncratic reactions. Any plant substance, whether used as food or medicine, has the potential to stimulate a negative response in unpredictably sensitive individuals. Safety classifications do not take into account such idiosyncratic responses, unless there is evidence to suggest that such an idiosyncratic reaction may be predictable.
- Allergic reactions. Certain plants in the Asteraceae, Apiaceae, and other plant families possess a relatively high degree of allergenicity, and specific mention of this is provided in the text for certain plants, such as feverfew herb (*Tanacetum parthenium*) and *Echinacea* spp. flowering tops. A plant's allergic potential, however, is not generally considered a basis for restrictive safety classification. Persons with a known allergy to ragweeds are nonetheless advised to observe caution in the consumption of all plants of the Asteraceae family, especially flowering parts.
- Contact dermatitis. The primary focus of this work is on herbal products for oral ingestion. Except in cases where there is a history of external therapeutic use, coupled with a record of associated dermatitis (e.g., mustard plasters), such concerns are beyond the scope of this document.
- Well-known toxic plants with known safety concerns that are not broadly traded. Many of the plants which are listed in standard toxicological texts as highly poisonous are not included in this document. Although isolates and constituents of some of these might be included in prescription drugs, they are not found in products which are otherwise accessible in a retail setting. Among the plants excluded are *Adonis vernalis*,

Claviceps purpurea, *Chondrodendron tomentosum*, *Colchicum autumnale*, *Conium maculatum*, *Croton tiglium*, *Datura* spp., *Gelsemium sempervirens*, *Hyoscyamus niger*, *Nicotiana* spp., *Rauwolfia* spp., *Stramonium* spp., *Strophanthus kombe*, and *Strychnos nux-vomica*.

- Homeopathic herbal preparations. Homeopathic products are classified as over-the-counter or prescription drugs and are regulated under the *Homeopathic Pharmacopoeia of the United States*. Safety concerns that arise for an herb in crude form may not apply to homeopathic preparations of the same herb, and this document does not address herbal products in homeopathic forms.
- Essential oils. Essential oils are concentrations of specific volatile compounds. While many essential oils have a well-documented history of safe use by appropriately skilled persons, they often present toxicological concerns that are absent or moderate in the crude plant materials from which the oil is derived. Except for a small number of essential oils that have a history of internal use, the classification of essential oils is beyond the scope of this document.
- Herbal products to which chemically defined active substances, including chemically defined isolated constituents of an herb, have been added. Safety of such products should be determined by manufacturers and marketers prior to market introduction.
- Environmental factors, additives, or contaminants. Classifications do not consider potential adulteration of botanical materials, although known adulterations that present health risks may be listed in an Editors' Note. Safety concerns of this sort must be addressed by the manufacturing practices of suppliers and manufacturers, who are responsible for assuring that herbal products are not contaminated or adulterated.

LITERATURE CITED

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Turner, N., and A. Szczawinski. 1991. *Common poisonous plants and mushrooms of North America*. Portland, OR: Timber Press.

WHO. 1991. WHO Guidelines for the assessment of herbal medicines. WHO/TRM/91.4. Geneva: World Health Organization.

ORGANIZATION OF DATA

Listings are alphabetically arranged by Latin name. More than one species of a genus are combined into a single listing in those cases where two or more species are used interchangeably, or where the issues relevant to safe use are the same or nearly the same for related species. Some herbs supply more than one useful part. These parts are listed and classified together only in those cases where the safety issues of all parts are sufficiently similar; otherwise, separate listings are included for each plant part.

Following the Latin name is the botanical family name. In instances where synonymous Latin names may be encountered in relevant references, one or more of these may be listed as a Synonym (**Syn).**

It is not unusual for a plant to have many common names, a fact which can confound the understanding of an herb's uses and potential safety concerns. AHPA published *Herbs of Commerce, 2nd edition* (McGuffin et al. 2000) to address this concern by assigning a single common or usual name to each herb, denoted in each listing in the current text as its standardized common name (**SCN**). Additional familiar common names are listed as other common names (**OCN**), though this field is generally not intended to be exhaustive. Ayurvedic names (**AN**) and pinyin names (**PN**) for botanical ingredients commonly used in Ayurvedic or traditional Chinese medicine are also included; note that Ayurvedic names tend to identify the plant itself, while pinyin names usually identify a specific plant part. With occasional exceptions, nomenclature in this work is derived from *Herbs of Commerce, 2nd edition*.

Following the plant's names is the **Part** of the plant for which the safety and interactions classifications that follow are made. Occasional specific information is included for those herbs that require special processing.

The remainder of each listing is divided into two sections, the **Quick Reference Summary**, which provides a concise, clinically relevant summary of the scientific information and traditional knowledge on the safety of each species or set of species, and the **Review Details** section, which provides details on the information presented in the summary.

Each entry's **Quick Reference Summary** includes the following elements. Each of the fields printed below in bold are always included, and state "None known" in the absence of any information relevant to the entry. All other fields are optional, and are included only for those entries for which information in the described area is relevant.

- Safety Class: Each entry is assigned one or more of the Safety Classes described earlier in this introduction.
- Interaction Class: Each herb is also assigned an Interaction Class as described previously.
- Contraindications: Any situations, conditions, or populations in which the botanical should not be used are listed here.
- Other Precautions: Special considerations for use are identified in this field. These may include, for example, common idiosyncratic effects (e.g., allergic reactions), adverse effects that may be undesirable but are not typically dangerous, or other conditions that require some specific caution, as stated.
- Drug and Supplement Interactions: This section gives details on known or suspected interactions in order to provide further information on any possible or probable interactions noted in an Interaction Class B or C. Note, however, that possible interactions that have low levels of evidence, or drugs for which a lack of interactions has been demonstrated, are generally listed under Pharmacological Considerations.
- Standard Dose: Quantitative dosage information is included here only for those plants listing a recommendation that excessive dosage be avoided. The dose is usually given in the quantity and form for direct consumption or for preparation as a tea or decoction and is based on the herb in its dried (dehydrated) form, unless otherwise stated. Equivalent dosage in the form of tinctures and extracts must be calculated based on the concentration of such extracts on a dry weight basis. Standard Dose should not be taken to be the equivalent of a dosage limitation. Rather, this dosage should be seen as related to the concept of "serving size." Although Standard Dose may be relevant to the determination of appropriate dosage limits, a thorough examination of other specific factors would be required prior to setting such levels.
- Notice: Certain plant constituents, such as caffeine or pyrrolizidine alkaloids, and herbs with known physiological actions, such as emetics and nervous system stimulants, may present safety considerations in numerous species. Rather than address such concerns in detail for each individual species, a Notice identifies these constituents

or actions and directs the reader to a thorough discussion of each such subject in Appendix 1, 2, or 3.

- Editors' Notes. Supplemental information relevant to the safe use of an herb, such as specific labeling recommendations, information regarding preparation, content of a chemical compound of potential concern, exceptions to use restrictions, possible adulteration, and other information are all included in this section, if required. Some discussion of the details, quality, or applicability of cited references may also be included here.
- Adverse Events and Side Effects. Recorded adverse changes in health, including any abnormal signs or symptoms, that have been reported to have occurred in association with the use of a particular herb are listed at this field. Side effects are defined as predictable effects of an herb that are not the principal effect for which the herb was taken (e.g., some people experience heartburn after ingestion of ginger). Adverse events, which include any health-related event associated with the use of a product that is perceived as harmful to the user, may or may not be related to an herb that was being taken at the time of an event. While some adverse events temporally associated with usage may be attributable to the herb consumed (e.g., nausea, vomiting, and central nervous system disturbances with overdose of raw *Ginkgo biloba* seed), many adverse events identified in case reports are not likely to be related to the associated herb. Sufficient detail is often lacking in case reports to determine whether a particular herb was likely the cause of any adverse event, and a case report cannot be considered to be in and of itself evidence that the reported adverse event was caused by the identified herb. All case reports in this text refer to human cases, unless they are listed under animal studies or otherwise specified.
- Pharmacological Considerations. If the physiological effects or other pharmacological activity of an herb may be relevant to the safe use of that herb, this information is reported here. Preference is given to data from human and animal use, although in vitro data that may be relevant to clinical use is also listed here. Low-level evidence for potential drug interactions is also typically included here.
- Pregnancy and Lactation. As available, information on the safety of herbs during pregnancy or while nursing is provided in this field. For a number of the Class 1 herbs, substantial data or traditional use suggests that these may be safely used in pregnancy and lactation. For other botanicals, less data and clinical experience are available regarding their use in pregnancy or lactation. The absence of formal data and clinical experience regarding the use of a botanical in pregnancy or lactation, in and of itself, was not justification to contraindicate the botanical in these conditions. In such cases, the editors and Expert Advisory Council have used their best judgment in conjunction with the available literature to make the most appropriate determination. The following statement is included in those entries for which data and clinical experience for the botanical were lacking or less robust than desired:

No information on the safety of this herb in pregnancy or lactation was identified in the scientific or traditional literature. Although this review did not identify any concerns for use while pregnant or nursing, safety has not been conclusively established.

The **Review Details** section for each entry is divided into five primary fields, each of which has its own organization. The reader will observe considerable redundancy when reading an herb's Quick Reference Summary and its Review Details sections together, as each of these is designed to be complete in itself. Thus, while the Quick Reference Summary provides enough information to understand an herb's safety and interaction profile, the Review Details section provides a more in-depth discussion of the data that was reviewed for the entry.

Some of the specific elements of this section are always present (again shown in bold font below) and when there is no relevant information known for a specific entry, that fact is affirmatively stated (e.g., "No clinical trials of drug or supplement interactions were identified."). All other elements are optional, and are again included only for those entries where information in the described area is relevant to the listing.

I. Drug and Supplement Interactions
   - Clinical trials of drug or supplement interactions
   - Case reports of suspected drug or supplement interactions
   - Animal trials of drug or supplement interactions

II. Adverse Events
   - Adverse events reported in clinical trials
   - Case reports of adverse events

III. Pharmacology and Pharmacokinetics
   - Human pharmacological studies
   - Animal pharmacological studies
   - In vitro pharmacological studies

IV. Pregnancy and Lactation
V. Toxicity Studies
- Acute toxicity
- Short-term toxicity
- Subchronic toxicity
- Chronic toxicity
- Genotoxicity
- Cytotoxicity

Each entry closes with a listing of the **Literature Cited** for that particular entry.

LITERATURE CITED

McGuffin, M., J. Kartesz, A. Leung, and A.O. Tucker. 2000. *Herbs of commerce. 2nd ed*. Silver Spring, MD: American Herbal Products Association.

DISCLAIMER

The editors and the Expert Advisory Council of the *Botanical Safety Handbook* have endeavored to ensure that the information contained in this document accurately represents contemporary knowledge on the safe use of herbal ingredients. In developing this work, particular care was given to identifying references that provide accurate information, and efforts were made to present a balanced view of all available scientific information.

The safe oral consumption of any substance can depend to a great deal on the health of an individual consumer, as well as to the quantity of the substance consumed. In addition, idiosyncratic or allergic reactions are often unpredictable. Any person who consumes an herb listed in this reference based on its classifications does so at his or her own risk, and should consult a healthcare provider in the event of an adverse response.

There is no obligation at this time for AHPA members to adopt the specific information contained here in their product labeling. Rather, this document is presented as a guideline, providing data to assist member and nonmember manufacturers in developing labels that fully inform consumers. Verification of all data and classifications for the purpose of label development is the responsibility of the manufacturer.

Abies balsamea (L.) Mill.

Pinaceae

SCN: balsam fir
OCN: American silver fir

Part: bark, needles, sap, wood

Quick Reference Summary

Safety Class: 1
Interaction Class: A

Contraindications

None known.

Other Precautions

None known.

Drug and Supplement Interactions

None known.

Adverse Events and Side Effects

None known.

Pharmacological Considerations

None known.

Pregnancy and Lactation

No information on the safety of balsam fir in pregnancy or lactation was identified in the scientific or traditional literature. Although this review did not identify any concerns for use while pregnant or nursing, safety has not been conclusively established.

Review Details

I. Drug and Supplement Interactions

Clinical Trials of Drug or Supplement Interactions

No clinical trials of drug or supplement interactions were identified.

Case Reports of Suspected Drug or Supplement Interactions

No case reports of suspected drug or supplement interactions were identified.

Animal Trials of Drug or Supplement Interactions

No animal trials of drug or supplement interactions were identified.

II. Adverse Events

Case Reports of Adverse Events

No case reports of adverse events were identified.

III. Pharmacology and Pharmacokinetics

Human Pharmacological Studies

No relevant human pharmacological studies were identified.

Animal Pharmacological Studies

No relevant animal pharmacological studies were identified.

In Vitro Pharmacological Studies

An ethanol extract of an unidentified part of balsam fir demonstrated in vitro mechanism-based inhibition of the drug metabolizing isoenzyme CYP3A4 (Tam et al. 2011).

IV. Pregnancy and Lactation

No information on the safety of balsam fir during pregnancy or lactation was identified.

V. Toxicity Studies

No toxicity studies were identified.

Literature Cited

Tam, T.W., R. Liu, J.T . Arnason, A. Krantis, W .A. Staines, P .S. Haddad, and B.C. Foster. 2011. Cree antidiabetic plant extracts display mechanism-based inactivation of CYP3A4. *Can. J. Physiol. Pharmacol.* 89(1):13-23.

A

Achillea millefolium L. — Asteraceae

SCN: yarrow
OCN: milfoil

Part: herb

Quick Reference Summary

Safety Class: 1
Interaction Class: A

Contraindications

None known.

Other Precautions

Persons with allergies to other members of the Asteraceae family (such as feverfew, chamomile, or *Echinacea* species) should exercise caution with yarrow, as allergic cross-reactivity is common to Asteraceae plants (Hausen 1996; Paulsen et al. 1993).

Drug and Supplement Interactions

None known.

Notice

Thujone (trace amounts) (Bradley 1992); *see* Appendix 1.

Editors' Notes

Use of yarrow as a food additive in the United States is subject to a limitation that the finished food or beverage is thujone-free (CFR 2011). Dietary ingredients for use in dietary supplements, however, are specifically excluded from the federal food additive definition (U.S.C. 2010).

Thujone is present in yarrow only in trace amounts (Leung and Foster 1996). Some concerns regarding the safety of thujone have been based on the effects of absinthe, an alcoholic beverage that historically contained thujone. Recent research, however, indicates that the alcohol content, rather than the thujone content, of absinthe was responsible for the reported adverse effects (Lachenmeier et al. 2006, 2008).

Adverse Events and Side Effects

Cases of contact allergy to yarrow plants have been reported, and allergic cross-reactivity to plants in the Asteraceae family has been documented (Davies and Kersey 1986; Guin and Skidmore 1987; Hausen 1996; Paulsen et al. 1993).

Pharmacological Considerations

In vitro studies with yarrow have reported inhibition of some CYP enzymes (Scott et al. 2006), increase in bile flow (Benedek et al. 2006), and estrogenic activity (Innocenti et al. 2007). One animal study showed some adverse effects on sperm at high doses (1.2 g/kg daily) but not at lower doses (Dalsenter et al. 2004).

Pregnancy and Lactation

Information on the safety of yarrow during pregnancy and lactation is limited. One animal study showed a decrease in fetal weight in offspring of rats administered high (2.8 g/kg) doses of yarrow, but no adverse effects were seen at lower doses (Boswell-Ruys et al. 2003).

No information on the safety of yarrow during lactation was identified. While this review did not identify any concerns for use while nursing, safety has not been conclusively established.

Review Details

I. Drug and Supplement Interactions

Clinical Trials of Drug or Supplement Interactions

No clinical trials of drug or supplement interactions were identified.

Case Reports of Suspected Drug or Supplement Interactions

No case reports of suspected drug or supplement interactions were identified.

Animal Trials of Drug or Supplement Interactions

No animal trials of drug or supplement interactions were identified.

II. Adverse Events

Case Reports of Adverse Events

Cases of contact allergy to yarrow have been documented (Davies and Kersey 1986; Guin and Skidmore 1987) and are believed to be caused primarily by the sesquiterpene lactone α-peroxyachifolid (Hausen et al. 1991).

In patch testing of Asteraceae-sensitive individuals, approximately 1.5% of 3800 test subjects were sensitive to yarrow (Hausen 1996). Similarly, patch testing of 686 subjects revealed 32 with sensitivity to several species of Asteraceae plants, including yarrow (Paulsen et al. 1993).

III. Pharmacology and Pharmacokinetics

Human Pharmacological Studies

No relevant human pharmacological studies were identified.

Animal Pharmacological Studies

No adverse effects on the male reproductive system were observed in male rats orally administered up to 600 mg/kg daily of an aqueous yarrow extract for 90 days. An increase in the percentage of abnormal sperm was observed in rats treated with 1.2 g/kg daily (Dalsenter et al. 2004).

In Vitro Pharmacological Studies

Inhibition of CYP450 isoenzymes CYP2C19, CYP19, and CYP3A4 by a methanolic extract of yarrow was observed in vitro (Scott et al. 2006).

A dose-dependent increase in bile flow was observed in isolated perfused rat livers treated with a polar fraction of yarrow (Benedek et al. 2006).

A methanol and water extract of yarrow demonstrated estrogenic activity in estrogen receptor-positive human breast cancer cells (MCF-7). Activation of estrogen receptors α and β was seen (Innocenti et al. 2007).

IV. Pregnancy and Lactation

A decrease in fetal weight was observed in offspring of rats administered 2.8 g/kg daily of an ethanolic extract of yarrow on gestational days 8 to 15, but no effects on fetuses were seen when yarrow was administered on GD 1 to 8. No changes in pre-implantation or post-implantation loss were observed (Boswell-Ruys et al. 2003).

No information on the safety of yarrow during lactation was identified.

V. Toxicity Studies

Acute Toxicity

The LD_{50} of both orally and subcutaneously administered yarrow extract (2% in propylene glycol and water) in mice is 1 g/kg (Provital 1998).

Chronic Toxicity

No signs of toxicity were observed in rats administered up to 1.2 g/kg daily of a yarrow aqueous extract for 90 days (Cavalcanti et al. 2006).

Genotoxicity

A weakly genotoxic effect of a yarrow aqueous extract was reported in *Drosophila melanogaster* (Graf et al. 1994).

Literature Cited

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Lachenmeier, D., D. Nathan-Maister, T. Breaux, et al. 2008. Chemical composition of vintage preban absinthe with special reference to thujone, fenchone, pinocamphone, methanol, copper, and antimony concentrations. *J. Agric. Food Chem.* 59(9):3073-3081.

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A

Achyranthes bidentata Blume — Amaranthaceae

SCN: achyranthes
PN: *niu xi* (root)
OCN: ox knee
Part: root

Quick Reference Summary

Safety Class: 2b, 2d
Interaction Class: A

Contraindications

Not for use in pregnancy except under the supervision of a qualified healthcare practitioner (Bensky et al. 2004; Chen and Chen 2004).

Not for use in excessive menstruation (Bensky et al. 2004; Chen and Chen 2004).

Other Precautions

None known.

Notice

Uterine stimulant (Bensky et al. 2004; Chen and Chen 2004); *see* Appendix 2.

Editors' Note

Multiple species are traded under the name *niu xi*, and all are contraindicated in pregnancy (Bensky et al. 2004).

Adverse Events and Side Effects

None known.

Pharmacological Considerations

None known.

Pregnancy and Lactation

Texts on traditional Chinese medicine indicate that achyranthes should not be used during pregnancy (Bensky et al. 2004; Chen and Chen 2004). Dilation of the cervical os was observed in association with achyranthes use in women who had abortions (Chen and Chen 2004). Animal studies of achyranthes have indicated anti-implantation, antifertility, and uterine stimulating activity (Che 1988; Chen and Chen 2004; Zhu and Che 1987).

No information on the safety of achyranthes during lactation was identified. While this review did not identify any concerns for use while nursing, safety has not been conclusively established.

Review Details

I. Drug and Supplement Interactions

Clinical Trials of Drug or Supplement Interactions

No clinical trials of drug or supplement interactions were identified.

Case Reports of Suspected Drug or Supplement Interactions

No case reports of suspected drug or supplement interactions were identified.

Animal Trials of Drug or Supplement Interactions

No animal trials of drug or supplement interactions were identified.

II. Adverse Events

Case Reports of Adverse Events

No case reports of adverse events were identified.

III. Pharmacology and Pharmacokinetics

Human Pharmacological Studies

No relevant human pharmacological studies were identified.

Animal Pharmacological Studies

In mice intraperitoneally administered polysaccharides from achyranthes at doses of 50, 100, or 200 mg/kg daily for 15 days, the 50 mg/kg dose inhibited the growth of introduced lung cancer tumors while the 200 mg/kg dose increased tumor growth. Tumor growth in mice administered 100 mg/kg was equivalent to that of the untreated control group (Jin et al. 2007).

Also see Pregnancy and Lactation for this entry.

In Vitro Pharmacological Studies

No relevant in vitro pharmacological studies were identified.

IV. Pregnancy and Lactation

Dilation of the cervical os was observed in association with achyranthes use in women who had abortions (Chen and Chen 2004).

A benzene extract of achyranthes saponins orally administered to mice at doses of 50 or 80 mg/kg reduced female fertility and implantation. The chloroform extract administered at doses of 80 or 120 mg/kg reduced fertility but did not affect implantation (Che 1988).

A dose-dependent decrease in fertility was observed in mice orally administered achyranthes saponins at doses of 125 to 1000 mg/kg (ED_{50} was 218 mg/kg). Implantation was prevented in mice orally administered 500 mg/kg of achyranthes saponins 5 days after mating, although no such activity was observed in rats administered 500 mg/kg. No

abortifacient activity was observed in rats orally administered 2 g /kg daily achyranthes saponins on days 14 to 19 after mating (Zhu and Che 1987).

Administration of achyranthes to mated female mice at doses of 250 to 500 mg/kg for 20 days resulted in a decrease in fertility and increased risk of miscarriage (Chen and Chen 2004).

Studies in rabbits and rats indicated that achyranthes stimulates uterine contractions (dose and route of administration not specified in English language translation) (Chen and Chen 2004).

No information on the safety of achyranthes during lactation was identified.

V. Toxicity Studies

Acute Toxicity

The LD_{50} of an orally administered combination of the compounds ecdysterone and inoteosterone in mice is 9 g /kg (Chen and Chen 2004).

Short-Term Toxicity

No abnormalities in blood parameters, liver, or kidneys were observed in mice orally administered an achyranthes decoction at a dose of 60 g/kg daily for 30 days (Chen and Chen 2004).

Literature Cited

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Aconitum carmichaelii Debeaux — Ranunculaceae

SCN: Sichuan aconite
PN: *chuan wu* (prepared main root); *fu zi* (prepared lateral root)

OCN: Japanese aconite
Part: prepared main and lateral root

Quick Reference Summary

Safety Class: 3
Interaction Class: A

Contraindications

Not for use except under the supervision of an expert qualified in the appropriate use of this substance (Bensky et al. 2004; Bisset 1981; Chan 2009; Fitzpatrick et al. 1994; Lin et al. 2004).

The unprepared root should never be taken internally (Bensky et al. 2004).

Other Precautions

References on traditional Chinese medicine indicate that alcohol should not be consumed with Sichuan aconite, as the absorption of the toxic constituents of Sichuan aconite will be greatly enhanced (Bensky et al. 2004; Chen and Chen 2004).

Drug and Supplement Interactions

Extreme caution is advised for use of Sichuan aconite in combination with antiarrhythmic medications (Chen and Chen 2004).

Editors' Notes

Both prepared and unprepared Sichuan aconite are available commercially. Sichuan aconite contains aconitine, a toxic alkaloid that affects the heart and the central nervous system (Bensky et al. 2004). Due to aconitine content, the unprepared root is highly toxic and is the primary herb associated with serious adverse events in traditional Chinese medicine hospitals in Hong Kong (Chan 2002; Chan et al. 1994a, 1994c; Poon et al. 2006). Processing of Sichuan aconite root greatly reduces the content of aconitine (Chen and Chen 2004). The prepared root, that has been processed to reduce toxicity, is the subject of this entry.

Sichuan aconite may be prepared in several ways, the most common of which is to cook the herb at boiling temperature for several hours. Such processing reduced the toxicity of Sichuan aconite to between 1/2000 and 1/4000 of the toxicity of the unprocessed herb (Chen and Chen 2004). Heat processing at temperatures above 120°C for 50 minutes decreased the diester alkaloids, such as mesaconitine, aconitine, and hypaconitine, and increased monoester alkaloids, such as benzoylmesaconine, benzoylaconine, and benzoylhypaconine, whereas heating to 105°C preserved the diester alkaloids (Taki et al. 1998).

A text on traditional Chinese medicine notes that while prepared Sichuan aconite is recognized to be toxic, if the appropriate dosage of the prepared root is combined with other appropriate ingredients such as ginger and licorice, and the patient is carefully instructed on the method of proper decoction, little likelihood of toxicity exists (Bensky et al. 2004).

Other species of *Aconitum* are also in trade (Bensky et al. 2004), and all should be considered class 3.

Adverse Events and Side Effects

Cases of aconite poisoning have been reported; some have been fatal. Characteristic symptoms of poisoning include nausea, vomiting, generalized paresthesia (numbness), irregular heartbeat, and cold extremities (Bisset 1981; Fitzpatrick et al. 1994).

A review of case reports of poisoning from various species of aconite indicated that the risk of poisoning is higher with inadequately processed aconite root, improperly prepared extracts (i.e., patients not boiling root as long as directed when making decoctions), large doses, and alcohol-based extracts (Lin et al. 2004).

Pharmacological Considerations

See Adverse Events and Side Effects above.

Pregnancy and Lactation

Traditional Chinese medicine texts contraindicate the use of prepared Sichuan aconite in pregnancy (Bensky et al. 2004; Chen and Chen 2004).

No information on the safety of prepared Sichuan aconite during lactation was identified. While this review did not identify any concerns for use while nursing, safety has not been conclusively established, and this substance is not recommended for use except under the supervision of an expert qualified in its appropriate use.

Review Details

I. Drug and Supplement Interactions

Clinical Trials of Drug or Supplement Interactions

No clinical trials of drug or supplement interactions were identified.

Case Reports of Suspected Drug or Supplement Interactions

No case reports of suspected drug or supplement interactions were identified.

Animal Trials of Drug or Supplement Interactions

No animal trials of drug or supplement interactions were identified.

II. Adverse Events

Case Reports of Adverse Events

Aconite poisoning has been reported to occur after mistaken use of the unprepared herb, inappropriate preparation, or overdose. Poisoning may affect the nervous system (dizziness, blurred vision, mydriasis, loss of vision, and numbness of mouth, limbs, or whole body), digestive system (severe nausea and vomiting), and circulatory system (palpitations, low blood pressure, cold extremities, chest pain, bradycardia, sinus tachycardia, ventricular ectopics, ventricular arrhythmias, and junctional rhythm) (Bisset 1981; Chan 2009; Fitzpatrick et al. 1994).

Toxic effects are caused by the alkaloid aconitine (Fu et al. 2006; Lin et al. 2004). Aconitine and other alkaloids activate the sodium channel and have widespread effects on the excitable membranes of cardiac, neural, and muscle tissues. Muscarinic activation also causes hypotension and bradyarrhythmias (Chang and But 1986).

A number of cases of aconite poisoning have been reported, most with typical clinical symptoms of aconite poisoning; some cases were fatal (But et al. 1994; Chan 2002; Chan et al. 1993, 1994a, 1994b, 1994c; Fatovich 1992; Fujita et al. 2007; Kolev et al. 1996; Lowe et al. 2005; Smith et al. 2005; Tai et al. 1992a, 1992b). Severe poisoning has been reported after consumption of as little as 0.2 mg of the compound aconitine or decoctions prepared from a Chinese herbal prescription containing 6 g of prepared Sichuan aconite (But et al. 1994). The toxic dose range is reported to be between 15 and 60 g of dried root prepared as a decoction, and is dependent on the time of harvest, method of preparation, and length of decocting time (Bensky et al. 2004).

A review of case reports of poisoning from various species of aconite indicated that the risk of poisoning is higher with inadequately processed aconite root, improperly prepared extracts (i.e., patients not boiling root as long as directed when making decoctions), large doses, and alcohol-based extracts (Lin et al. 2004).

III. Pharmacology and Pharmacokinetics

Human Pharmacological Studies

No relevant human pharmacological studies of prepared Sichuan aconite were identified.

Animal Pharmacological Studies

A dose-dependent decrease in plasma glucose levels was seen in diabetic rats orally administered up to 50 mg/kg prepared Sichuan aconite. The plasma glucose-lowering effect was eliminated by blockage of μ-opioid receptors (Liou et al. 2006).

In mice orally administered 1 mg/kg daily of the compound aconitine, various types of arrhythmias were observed including ventricular fibrillation, ventricular tachycardia, and bundle branch block. The arrhythmias occurred within 30 minutes of administration of aconitine,

and persisted after 90 min. The concentration of aconitine in organs and blood gradually decreased after repeated administration, such that on day 22 of the study, transient ventricular tachycardia and bundle branch block were rarely observed. Twenty percent of mice died in the first 2 days of the study, presumably due to aconitine poisoning (Wada et al. 2005).

A decrease in urine taurine and trimethylamine *N*-oxide (TMAO) and increase in urine citrate, 2-oxoglutarate, succinate, and hippurate were observed in rats administered an aqueous extract of prepared Sichuan aconite at a dose of 18, 36, or 88 g/kg daily for 14 days (Li et al. 2008).

In Vitro Pharmacological Studies

A study in rat liver microsomes suggested that the compound aconitine may be metabolized by CYP3A and CYP1A1/2 (Cao et al. 2001).

IV. Pregnancy and Lactation

Traditional Chinese medicine texts indicate that prepared Sichuan aconite is contraindicated in pregnancy (Bensky et al. 2004; Chen and Chen 2004).

No malformations were found in fetuses of rats treated with doses up to 10.3 g/kg prepared Sichuan aconite, although the body weight and food consumption were reduced in the pregnant rats. Fetuses of rats administered 8.3 g/kg of *Aconitum kusnezoffii* had a reduction in body length and breastbone calcification (Xiao et al. 2005). The dosage form and route of administration used in this study was not specified in the English language abstract but is likely to have been a decoction administered orally (Xiao et al. 2005).

In rat embryos treated with the compound aconitine at doses of 0, 1, 2.5, 5, or 10 µg/ml, with or without S9 mix, embryonic growth and development were adversely affected at the concentration of 2.5 µg/ml aconitine without S9 mix. Effects included reduced crown-rump length and head length, decreased number of somites, and lower morphologic score. When the concentration of aconitine was increased to 5 µg/ml, severe dysmorphogenesis effects were observed, including cardiac defects, irregular somites, and brain malformation (Xiao et al. 2007).

No information on the safety of prepared Sichuan aconite during lactation was identified.

V. Toxicity Studies

Acute Toxicity

The LD_{50} of prepared Sichuan aconite is 161 g/kg from oral administration and 3.5 g/kg from intravenous administration (Chen and Chen 2004). The LD_{50} of unprepared Sichuan aconite in mice is 5.49 g/kg from oral administration and 0.49 g/kg from intravenous administration (Chen and Chen 2004). The LD_{50} of orally administered Sichuan aconite root is approximately 10 g/kg in rats and over 10 g/kg in mice (Minematsu et al. 1996).

The lethal human dose of the compound aconitine is reported as 3 to 6 mg (Frohne and Pfänder 1983).

Short-Term Toxicity

In mice intraperitoneally administered a decoction of Sichuan aconite or *Aconitum kusnezoffi*, at doses of 40, 200, or 400 mg/kg, no changes in liver or kidney parameters were seen at a dose of 40 mg/kg, while at doses of 200 or 400, high serum levels of lactate dehydrogenase were observed along with histological changes in the liver and kidney, but no significant changes in heart or gonads were seen (Chan et al. 1995).

Myelo-optic neuropathy was observed in rabbits intraperitoneally administered a tincture of *Aconitum* spp. containing 0.6 mg/kg total alkaloids (Suk et al. 1994).

In rats orally administered prepared Sichuan aconite daily for 5 weeks, the nontoxic level was estimated to be over 2.5 g/kg daily (Minematsu et al. 1996).

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Acorus calamus L. — Acoraceae

SCN: calamus
AN: *vacha*
OCN: acorus; sweet calamus; sweetflag

Part: rhizome of the asarone-containing triploid or tetraploid varieties

Quick Reference Summary

Safety Class: 3
Interaction Class: A

Contraindications

Not for use except under the supervision of an expert qualified in the appropriate use of this substance (Chadha 1988; De Smet 1985; Leung and Foster 1996; Martindale and Reynolds 1996; Wichtl 2004).

Other Precautions

None known.

Drug and Supplement Interactions

None known.

Notice

Alkenylbenzenes (β-asarone and α-asarone) (usually 1.1–2.6%; up to 8.0%) (Hanson et al. 2005; Kumar et al. 2000; Motley 1994; Oprean et al. 1998; Subramanian et al. 2004; Widmer et al. 2005); *see* Appendix 1.

Editors' Notes

Calamus grows wild in India, China, Europe, and North America, and the chemical composition of the plant material

varies according to origin. The essential oil of plants from India contains up to 75% β-asarone (*see* Alkenylbenzenes in Appendix 1), while the oil of calamus from Japan and eastern Russia contains 10–40%, oil from European plants contains approximately 13%, and that from North America contains almost no β-asarone (Keller and Stahl 1982, 1983; Raina et al. 2003; Stahl and Keller 1981; Subramanian et al. 2008). Since varieties of calamus may not be well differentiated in commerce, the caution stated for the Asian and European varieties should be considered relevant to any sample that is not positively identified as the North American variety.

Animal and in vitro studies have indicated that the compound β-asarone has carcinogenic, mutagenic, and chromosome-damaging properties (Abel 1987; Balachandran et al. 1991; FAO/WHO 1981; Goggelmann and Schimmer 1983; Habermann 1971; Hasheminejad and Caldwell 1994).

All varieties of calamus are prohibited in foods in the United States (CFR 2011).

Adverse Events and Side Effects

None known.

Pharmacological Considerations

A reference text on traditional Chinese medicine indicated that overdose and long-term use of calamus should be avoided (Bensky et al. 2004).

Pregnancy and Lactation

A study with calamus essential oil in chicken eggs showed no adverse effects on embryo development (Yabiku et al. 1979). No other information on the safety of calamus in pregnancy or lactation was identified.

While this review did not identify any concerns for use while pregnant or nursing, safety has not been conclusively established, and this substance is not recommended for use except under the supervision of an expert qualified in its appropriate use.

Review Details

I. Drug and Supplement Interactions

Clinical Trials of Drug or Supplement Interactions

No clinical trials of drug or supplement interactions were identified.

Case Reports of Suspected Drug or Supplement Interactions

No case reports of suspected drug or supplement interactions were identified.

Animal Trials of Drug or Supplement Interactions

Extracts of calamus have been shown to potentiate pentobarbitone-induced sleeping time (Dandiya et al. 1959; Hazra et al. 2007; Panchal et al. 1989).

II. Adverse Events

Case Reports of Adverse Events

A 19-year-old man experienced diaphoresis, persistent vomiting, and mild leukocytosis after ingesting an 8-inch-long calamus rhizome (Vargas et al. 1998).

III. Pharmacology and Pharmacokinetics

Human Pharmacological Studies

No relevant human pharmacological studies were identified.

Animal Pharmacological Studies

An ethanolic extract of calamus demonstrated immunomodulatory potential by inhibiting proliferation of mitogen- and antigen-stimulated human peripheral blood mononuclear cells. The extract inhibited growth of several mouse and human cell lines (Mehrotra et al. 2003).

Animal studies have indicated that calamus has a depressant effect on the central nervous system (Agarwal et al. 1956; Dandiya et al. 1958, 1959; Dandiya and Cullumbine 1959; Dasgupta et al. 1977).

In Vitro Pharmacological Studies

Negative ionotropic and chronotropic effects were observed in frog heart preparations treated with concentrations of 100 µg/ml of an alcohol extract of calamus (Panchal et al. 1989).

IV. Pregnancy and Lactation

No teratogenic effects were observed in chicken eggs injected with calamus essential oil at doses of 0.12, 0.60, 3.00, 15.00, or 75.00 mg/egg (Yabiku et al. 1979). Similarly, no teratogenic effects were observed in chicken eggs injected with α-asarone at doses up to 4 mg/egg. In eggs injected with β-asarone, 43% of embryos survived a dose of 0.04 mg/egg, while none survived a dose of 4 mg/egg (Yabiku et al. 1979).

No information on the safety of calamus in lactation was identified.

V. Toxicity Studies

Acute Toxicity

The LD_{50} of orally administered calamus oil in rats was 0.77 g/kg for oil from Jammu (~75% β-asarone) (Jenner et al. 1964), 4.3 g/kg for oil from Kashmir (~5% β-asarone) (WHO 1981), and 3.5 g/kg for oil from Europe (~5% β-asarone) (WHO 1981).

The LD_{50} of intraperitoneally administered European calamus oil in mice was 1.1 g/kg for oil containing β-asarone and 1.7 g/kg for oil with no β-asarone (Yabiku et al. 1979). In rats, the intraperitoneal LD_{50} of the essential oil was 299 mg/kg (Yabiku et al. 1979). The LD_{50} of intraperitoneally administered β-asarone in mice was 0.184 g/kg (Yabiku et al. 1979).

Chronic Toxicity

In rats fed diets containing 0, 500, 1000, 2500, or 5000 ppm (0, 0.05, 0.1, 0.25, and 0.5%) Jammu calamus essential oil (~75% β-asarone) daily for 2 years, all of the 5000 ppm group died within 45 weeks, all of the 2500 ppm group died within 68 weeks, and all of the 1000 ppm group died within 104 weeks. Gross abnormalities were observed, including liver damage, fluid in the pleural and or peritoneal cavity, and tumorous masses in the intestines. Cardiac atrophy was observed in both test and control animals but was more severe in test animals (Taylor 1967, 1981).

In rats fed diets containing 0.1, 0.5, 1.0, or 2.0% European calamus essential oil (~5% β-asarone) daily for 2 years, leiomyosarcomas, hepatocellular adenomas, and hepatocellular adenocarcinomas were observed at the 1 and 2% dose levels. Other dose-dependent adverse effects on the livers were observed, with effects at the 0.1% dose being similar to those in the controls, or slightly increased. Dose-dependent changes observed in the heart included myocardial atrophy, fibrosis, fatty degeneration, and fatty infiltration (Taylor 1981).

In rats fed diets containing 0, 400, 800, or 2000 ppm (0, 0.04, 0.08, or 0.2%) β-asarone for 2 years, none of the animals receiving 2000 ppm β-asarone survived more than 84 weeks, and mortality was increased at the 800 ppm dose. Gross pathological changes were observed and included serous fluid in the abdominal and pleural cavities, liver and kidney changes, and tumorous masses in the intestinal tract. Occurrence of tumors was dose-related. Changes in the heart included myocardial atrophy, fibrosis, thrombosis, fatty degeneration, and fatty infiltration (Taylor 1981).

Genotoxicity

No mutagenic activity of a calamus extract was observed in *Salmonella typhimurium* strains TA97a, TA100, TA102, and TA104. Dose-dependent antimutagenic activity was observed at concentrations of 25 to 100 µg/plate (Aqil et al. 2008).

The compound *cis*-asarone has shown mutagenic activity in vitro (Goggelmann and Schimmer 1983), although this activity has been characterized as weak in comparison with other mutagenic/carcinogenic natural substances (Wichtl 2004).

No mutagenic activity of β-asarone was observed in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, or TA1538 at concentrations of 2 to 200 µg/plate with metabolic activation. Tests without metabolic activation were not completed (Hsia et al. 1979).

No mutagenic activity of α-asarone was observed in the Ames test with *Salmonella typhimurium* at concentrations of up to 5000 ppm with or without activation. In a related study, β-asarone was not mutagenic at 50 ppm, but did show mutagenic activity at a concentration of 5000 ppm with activation (Yabiku et al. 1979).

Cytotoxicity

An ethanol extract of calamus demonstrated cytotoxic activity in a brine shrimp lethality test (Padmaja et al. 2002).

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