The Handbook of Clinically Tested Herbal Remedies

Volume 1

Part I: Fundamentals of Herbal Medicine
Part II: Methods
Part III: Botanical Profiles—
Product and Clinical Trial Information
(Artichoke–Ginseng)

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Editor

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Preface

> I believe that if herbal medicine is to play a significant role in future health care, the therapeutic effects of the individual herbs must be carefully evaluated by well-designed, randomized, double-blind, placebo-controlled studies involving a significant number of human subjects.
>
> Varro E. Tyler (1999)
> "Phytomedicines: Back to the Future"
> In *Journal of Natural Products*

Background of the Project

The genesis of the idea for this book came from a conversation with my childhood physician, Larry Posner, MD, at a party in September 1998. He told me of his interest in botanicals due to the number of patients he had taking dietary supplements and of the limited knowledge he had of those products. He knew of my work with medicinal herbs and asked me to speak to him in his language regarding the evidence for these herbs. I inquired what language that might be and he replied, "double-blind, controlled, randomized clinical trials." My response was that quite a few studies have been conducted on herbal remedies, probably more than he realized. Thus, the idea of this book was born.

Purpose and Scope of the Book

This book provides consumers and health professionals with a means to distinguish those herbal products that have the backing of clinical evidence to substantiate claims of efficacy. It includes product descriptions provided largely from label information. In addition, this book describes in detail the trials associated with those products and provides an assessment of the quality of those trials.

Only products that have undergone controlled clinical trials are included, as this research design is considered the most persuasive and is generally given the most weight by researchers and practitioners. Many herbal preparations commonly sold on the market are not included in this text, as they have not been subjected to controlled clinical trials.

The book lists products, made with 32 herbs and ten formulas, that have been studied in a total of 369 clinical trials. Attempts were made to be systematic and inclusive in gathering products and trials; however, due to the magnitude of the effort and the amount of time required to complete the project, I acknowledge that it is essentially a snapshot—a sampling of the existing products and their clinical trials at the time when we were doing research for the book.

It is my hope that this snapshot will assist in the evaluation of the clinical science behind botanical medicine and will help with the evaluation of the evidence for herbal product efficacy. I also hope that this book will help to bridge the gap between herbal medicine and standard Western therapies by using the language of the latter to describe the former. Ultimately it is my desire that this book will assist in establishing an appropriate place for botanical medicine alongside standard Western therapies in the medicine cabinet.

The chapters in *Part I: Fundamentals of Herbal Medicine* provide background as well as context for the product and trial summaries that follow. These chapters provide information on the regulatory status of botanicals in the United States, the characterization and standardization of products, as well as the means to establish bioavailability, efficacy, and safety. Also included is a discussion on the "borrowing" of science from one product to support claims of efficacy for another. In addition, there is a discourse on the motives for conducting trials in the United States and in Europe, particularly in Germany. Finally, a chapter on pharmacopoeial monographs describes what they are and what information they provide.

Part II: Methods describes the methods used to gather information on products and clinical studies. It includes the criteria for entry into the book and the means used to evaluate the efficacy of the individual trials.

Part III: Botanical Profiles contains information on products and clinical trials. Products are grouped according to the principal botanical ingredient. If the products are multi-ingredient formulas, without

a primary ingredient, then they are listed separately. Each botanical section is headed by a summary review of the products and trials. This summary section contains an at-a-glance table listing the products included in that section, the indications addressed by the clinical studies, and the number and quality of those studies. The summary section also includes information from therapeutic monographs with use information for that herb. The summary section is followed by details on the products, which is in turn followed by a detailed account of the clinical trials for each product.

Indexes allow for easy access to the product and trial information through the botanical common and scientific names, as well as by product and manufacturer names and therapeutic indication.

Chapter 1

History and Regulation of Botanicals in the United States

Loren D. Israelsen
Marilyn Barrett

INTRODUCTION

At least four regulatory classifications are now possible for botanicals in the United States: (1) food, (2) dietary supplement, (3) over-the-counter (OTC) drug, and (4) prescription (Rx) drug. However, most botanical products are regulated as dietary supplements according to provisions in the Dietary Supplement Health and Education Act (DSHEA) of 1994. This chapter gives a brief description of how botanicals were historically regulated in the United States, the subsequent genesis of DSHEA, and the means that DSHEA provides to regulate herbs and other botanicals. It also briefly covers the regulations regarding botanicals as drugs, either sold without a doctor's prescription over-the-counter or requiring a doctor's prescription.

HISTORY

Plants have, at one time, supplied virtually all cultures with food, clothing, shelter, and medicines. It is estimated that approximately 10 to 15 percent of the roughly 300,000 species of higher plants have a history of use in traditional medicine. By contrast, only 1 percent of plant species have a history of food use (McChesney, 1995).

One hundred years ago, herbs were well established as medicines in the United States. They were widely listed in the *United States*

Pharmacopeia (USP) and prescribed by physicians. Herbal tinctures, extracts, salves, and so forth, were the materia medica of the day.

Regulation of medicines in this country began when the authority to set and enforce drug safety standards was given to the Food and Drug Administration (FDA) in 1938. The passage of the Food, Drug, and Cosmetic Act gave the FDA the responsibility to prosecute the adulteration or misbranding of foods, drugs, and cosmetics.

Herbal preparations soon gave way to single-entity chemical drugs. World War II created a demand for more powerful drugs of all kinds, particularly antibiotics and trauma treatment agents. The federal government urged drug companies, then largely botanical crude-drug houses, such as Merck, Lily, and Parke-Davis, to invest in new synthetic chemistry-based research. Single-entity chemicals were more consistent, easier to measure, and judged more specific in their therapeutic focus than botanical preparations.

In 1951, Congress passed the Durham-Humphrey Act which defined a prescription drug as any drug that because of its toxicity or other potential for harmful effect or method of use is not safe for use except under the supervision of a practitioner licensed by law to administer such a drug (Young, 1995). Manufacturers at that time had to position their drugs as either Rx or OTC.

In 1962, the Food, Drug, and Cosmetic Act was expanded to require all drugs marketed at that time to be proven *both* safe and effective. The FDA then issued guidelines for safety and efficacy testing requirements for new drugs. As a result, new drugs now required the FDA's approval before marketing. Old drugs were permitted to remain on the market as long as their ingredients and labeling remained unchanged.

In 1972, the FDA began a comprehensive review of all OTC drug products to assess their safety and efficacy. Drug ingredients found to be generally recognized as safe and effective (GRASE) were placed into Category I and approved for marketing. Those determined to be unsafe or ineffective were placed in Category II and banned from use in any OTC drug. If safety and efficacy could not be determined due to a lack of information, then the ingredient went into Category III. With few commercial sponsors to conduct safety and efficacy studies, many botanicals, listed as possible or known ingredients in OTC products, were relegated to Category II status and some were placed in Category III. With few herbs retaining drug status after the OTC re-

view, the botanical industry had no other regulatory option but to offer their products as foods.

In the late 1970s, the FDA began to apply the food additive provisions of the Food, Drug, and Cosmetic Act to botanicals. Under provisions added to the Federal Food, Drug, and Cosmetic Act of 1958, food additives already on the market in 1958 were accepted without FDA review. However, substances added to the food supply after this date were required to gain FDA approval prior to marketing, unless they were considered GRAS (generally recognized as safe). A fair number of herbs were included on a list of GRAS food additives that had been prepared by the Flavor and Extract Manufacturers Association as flavorings for alcoholic beverages. However, the FDA viewed commonly used herbs as unapproved food additives and therefore subject to FDA approval prior to marketing. This interpretation led to a series of bitterly fought court cases and several herbs being taken off the market.

Congress passed the Nutrition Labeling Education Act of 1990 (NLEA) to reform food labeling and to allow, for the first time, a new class of health claims based on disease-nutrient relationships. For the most part, this legislation did not apply to botanicals because of the way it was written and the way it was interpreted by the FDA.

With lawsuits between herbal manufacturers and the FDA commonplace, a group of leading herb companies met with Senator Orrin G. Hatch (R-Utah) and Congressman Bill Richardson (D-New Mexico) who drafted legislation that became the Dietary Supplement Health and Education Act of 1994. This law was passed by Congress and signed into law by President Clinton on October 25, 1994. This was the first time a U.S. law defined the terms *herb* or *botanical*.

DSHEA EXPLAINED

As with most federal laws, the legislative language of DSHEA is arcane, if not mystifying. The core provisions of the act, however, are straightforward and create an expansive framework for all dietary supplements. The following summary of DSHEA is an "herbs-only" interpretation which provides a useful tool for those wishing to see how DSHEA creates a new architecture for the manufacture, sale, and promotion of herbs.

Definition

DSHEA defines the term *dietary supplement* as an herb or other botanical or concentrate, constituent, extract, or combination of any botanical that is intended for ingestion as a tablet, capsule, or liquid, is not represented for use as a conventional food or as a sole item of a meal or the diet, and is labeled as a dietary supplement. This includes new drugs that were marketed as botanicals prior to such approval; it does not include a botanical approved as a new drug, or authorized for investigation as a new drug, and not previously marketed as a dietary supplement. Botanicals are not classified as food additives.

Safety

Dietary supplement products are allowed to contain botanicals that have been present in the food supply and in a form in which the food (botanical) has not been chemically altered. Dietary supplement ingredients marketed in the Unites States before October 15, 1994, are regarded as safe because of their long history of use. Those ingredients not marketed before then are "new" ingredients. At least 75 days before introduction into commerce, manufacturers must provide the FDA with information that shows the new botanical can reasonably be expected to be safe under conditions of use or labeling.

DSHEA states that a botanical is considered unsafe under one of two conditions: (1) it presents a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling, or (2) it is a new botanical for which inadequate information exists to provide reasonable assurance that it does not present a significant or unreasonable risk of illness or injury. In any case, the FDA shall have the burden of proof to show that a botanical is unsafe.

Good Manufacturing Practices

A botanical is also considered unsafe if it is prepared, packed, or held under conditions that do not meet current good manufacturing practice regulations (GMPs). For the moment, the preparation and packaging of dietary supplements is covered by the same GMPs that apply to conventional foods. However, DSHEA authorizes the FDA to establish separate GMPs for dietary supplements, and rule making by the FDA is imminent.

Labeling

The label must identify the product by the term *dietary supplement*. Botanical dietary supplement labels must list the name of each ingredient, the quantity of such ingredients, or, if a proprietary blend, the total quantity of all ingredients. The label must also identify any part of the plant from which the ingredient is derived.

Botanical dietary supplements are misbranded if they are represented as conforming to such official compendium as *USP* and fail to do so, fail to have the identity and strength which they represent to have, or fail to meet the quality, purity, or compositional specifications, based on validated assays or other appropriate methods, which they are represented to meet.

Literature, including an article, a chapter in a book, or an official abstract of a peer-reviewed scientific publication which appears in an article shall not be defined as labeling when used in connection with the sale of botanicals to consumers provided that it is not false or misleading, does not promote a particular manufacturer or brand of botanical, is displayed or presented with other items on the same subject matter so as to present a balanced view of the available scientific information on a botanical, and, if displayed in an establishment, is physically separate from the botanical and does not have appended to it a sticker or other method that associates it with the product.

Claims of Benefit or "Statements of Nutritional Support" Allowed in Labeling

Under DSHEA, a statement for a botanical dietary supplement may be made if the statement describes how a botanical is intended to affect the structure or function of humans, characterizes the documented mechanism by which a botanical acts to maintain such structure or function, or describes general well-being from consumption of a botanical. The statement must contain, prominently displayed and in bold-faced type, the following: "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease."

The FDA published a final rule in the Federal Register on February 7, 2000 (docket No. 98N-0044), which describes how the agency will distinguish disease claims from structure/function claims. The rule

permits health maintenance claims ("maintains a healthy circulatory system"), other nondisease claims ("for muscle enhancement," "helps you relax"), and claims for common, minor symptoms associated with life stages ("for common symptoms of PMS," "for hot flashes"). It does not allow for claims regarding diseases ("prevents osteoporosis") or implied disease claims ("prevents bone fragility in postmenopausal women") (FDA, 2000).

As with all food labeling, statements must be truthful and not misleading. Statements of nutritional support may be made without prior FDA review, but the manufacturer must notify the FDA within 30 days of marketing a product with a new claim and must have substantiation for the claim. Criteria for substantiating a claim are not yet defined by the FDA. However, advertising guidelines for benefit statements for dietary supplements have been published by the Federal Trade Commission (1998) and can be found on their Web site (www.ftc.gov).

DSHEA establishes that a botanical is not a drug solely because its label or labeling contains a statement of nutritional support. Also, a botanical shall not be deemed misbranded if its label or labeling contains directions or conditions of use or warnings.

Commission on Dietary Supplement Labels

DSHEA established a presidential commission to study and provide recommendations for the regulation of label claims and statements for botanicals, including the use of literature in connection with the sale of botanicals, and procedures for evaluation of such claims. The seven members of the Commission on Dietary Supplement Labels were appointed by the president to evaluate how best to provide truthful and scientifically valid information about dietary supplements to consumers. The commission's final report, which was submitted to the president and Congress in November 1997, included guidance regarding statements of nutritional support and the substantiation of such claims. The commission recognized that under DSHEA, botanical products should continue to be marketed as dietary supplements, when properly labeled. However, they recommended that a review panel be established to review claims for OTC drug uses (Commission on Dietary Supplement Labels, 1997).

Office of Dietary Supplements

DSHEA also established an Office of Dietary Supplements (ODS) within the National Institutes of Health (NIH). The purposes of the office are to explore the potential ability of botanicals to improve health care and to promote scientific study of the benefits of botanicals in maintaining health and preventing chronic disease.

The director of the ODS is to conduct and coordinate scientific research relating to botanicals that can limit or reduce the risk of diseases such as heart disease, cancer, birth defects, osteoporosis, cataracts, or prostatism, collect results of scientific research related to botanicals and compile a database, and serve as a principal advisor to the NIH, the Centers for Disease Control and Prevention (CDCP), and the commissioner of the FDA on issues relating to botanicals and scientific issues arising in connection with the labeling and composition of botanicals.

Currently the ODS, in collaboration with the National Center for Complementary and Alternative Medicine (NCCAM), sponsors six botanical research centers. The ODS Web site hosts two databases: one containing information regarding federally funded research on dietary supplements (CARDS, "Computer Access to Research on Dietary Supplements") and the other containing scientific literature regarding dietary supplement ingredients (IBIDS, "International Bibliographic Information on Dietary Supplements") (http://dietary-supplements.info.nih.gov). The ODS is also conducting systematic reviews of the literature in order to determine areas needing research and to assist in the development of clinical guidelines. Fact sheets with information on the most commonly used botanicals are in preparation. The ODS, again in conjunction with NCCAM, has sponsored clinical trials on St. John's wort and ginkgo. Several dozen other trials on botanicals are currently listed on the NCCAM Web site (nccam. nih.gov). The ODS is also currently supporting the development of validated analytical methods, standards, and reference materials for the most commonly used botanicals.

DRUGS: OTC AND Rx

Before a botanical product is marketed as a drug with a claim to diagnose, treat, cure, or prevent a disease, it must first be approved by the FDA. The revision of the Food, Drug, and Cosmetic Act in 1962 required all drugs marketed after that time to be proven both safe and effective. This revision presented the FDA with the challenge of updating its approval of hundreds of drugs already on the market that had not been proven effective. The FDA set up panels of experts to review the active ingredients of these drugs, many of which were sold over-the-counter. However, many herbal products were found to be either unsafe, ineffective, or simply lacking sufficient evidence to evaluate (Tyler, 1993).

In order to obtain drug status for a new botanical product, or for one that failed a previous evaluation, manufacturers must submit a New Drug Application (NDA) to the FDA. This requirement holds whether the new drug is to be sold as an OTC or Rx drug. The NDA must contain evidence of the product's safety and efficacy. This evidence is usually in the form of pharmacological studies, ranging in scope from in vitro assays and small animal studies to randomized, double-blinded clinical trials in humans, with an emphasis on the clinical studies. The benefit to pharmaceutical firms which manufacture synthetic chemical drugs is that their research is rewarded by patent protection for a substantial period of time. However, as most herbs have previously been marketed in a traditional form, and thus are not new or unique, they are not eligible for patent protection. There are some exceptions when a botanical is prepared in a unique form (for example, the ginkgo extract EGb 761) or for a previously unknown use. Without patent protection, most manufacturers are unwilling to spend the money necessary to conduct the research required for a new drug application. In addition, manufacturers may find it easier to forego scientific studies as they can easily sell their products as dietary supplements.

The Commission on Dietary Supplement Labels (1997) recommended that the FDA establish a "review panel for OTC claims for botanical products that are proposed by manufacturers for drug uses" (p. 57). However, in April 1998 the FDA published a notice responding to the commission report, indicating that the agency considers

such a review to be "premature" at this time. The FDA did not give an explanation for their decision (FDA Notice, 1998).

Petitions formally requesting that valerian and ginger be recognized as old OTC drug ingredients were filed with the FDA in 1994. Nearly six years later, the agency issued a response provisionally accepting the supporting data, which was largely European, but only under very stringent conditions. Valerian and ginger have yet to become OTC drugs.

Numerous experts agree that a select number of botanicals are proper candidates for OTC drug status. Although this would mean that some plant extracts would be available both as dietary supplements and OTC drugs, it is likely that many American consumers who currently would not use a certain herb as a dietary supplement would accept and use that same herb if it were offered as a drug that has received FDA (government) approval. Likewise, physicians, pharmacists, and other health care providers would be far more inclined to recommend, or at least not discourage, the use of an herbal OTC drug. The reasons being that OTC drugs are manufactured under stricter good manufacturing practices, and OTC products have mandatory labeling which includes dosage recommendations, cautions, and warnings. Although manufacturers of botanical products are welcome to submit their products for review under the new drug approval process, it does not appear that the FDA is prepared to actively welcome OTC applications for botanicals as old drug ingredients. That is, for a botanical to achieve OTC status, it must have all the scientific research required for a new drug. It is unlikely to be "grandfathered in" as an old drug without that documentation.

PROSPECTUS

Canada has created a natural health products category, which is intermediate between the formal OTC drug review process and the less formal dietary supplement regime in the United States. Many in the herbal industry now feel that such a category would be beneficial for the United States as well. However, this would require a new regulatory category to be created.

In the meantime, it is entirely possible for a botanical to be marketed and sold as a food, a dietary supplement, and a drug at the same

time, depending on its label claim. For example, ginger root can be sold as a food ingredient, as a dietary supplement "to maintain a calm stomach," or (if approved by the FDA) as an OTC drug "to prevent and treat nausea or motion sickness."

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Artichoke

Other common names: **Cynara, globe artichoke**
Latin name: ***Cynara scolymus* L.** [Asteraceae]
Plant part: **Leaf**

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

Artichokes were greatly valued by the ancient Greeks (fourth century B.C.) for treating digestive disorders. Clinical studies have been conducted on aqueous extracts of the leaves. The extracts characteristically contain caffeoylquinic acid derivatives, including caffeic acid, chlorogenic acid, and cynarin (1,5-dicaffeoylquinic acid) (Kraft, 1997).

Cynara-SL™ contains 320 mg per capsule of a dried aqueous extract called LI 120, with an herb-to-extract ratio of 3.8 to 5.5:1. It is manufactured in Germany by Lichtwer Pharma AG and distributed in the United States by Lichtwer Pharma U.S., Inc. This extract is marketed in Europe as Hepar-SL forte®.

Valverde Artischocke, which is manufactured by Novartis Consumer Health GmbH in Germany, is not provided in the United States. The tablets contain 450 mg of a dried aqueous extract called CY-450 with a ratio of 25 to 35:1.

ARTICHOKE SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
Cynara-SL™ (US), Hepar-SL forte ® (EU)	Lichtwer Pharma AG, Germany/ Lichtwer Pharma U.S., Inc.	Aqueous extract (LI 120)	6 capsules, 1.92 g (intraduodenally)	Choleresis (bile secretion)	1	MOA (III-1)
Valverde Artischocke (EU)	Novartis Consumer Health GmbH, Germany/None	Aqueous extract (CY450)	2 tablets twice daily (1.8 g extract/day)	Hyper-lipoproteinemia (elevated cholesterol levels)	1	Yes (I-1)

SUMMARY OF REVIEWED CLINICAL STUDIES

Artichoke preparations may relieve digestive complaints through increases in the formation and flow of bile. The increased flow of bile is called choleresis. Bile is excreted from the liver, stored in the gallbladder, and released into the intestine. Bile acids form a complex with dietary fats in the intestine and thereby assist in their digestion and absorption (Kraft, 1997).

In addition, stimulation of bile production results in reduced serum cholesterol, as cholesterol is pulled from the blood to be converted into bile acids. The increased flow of bile may also be beneficial for patients with irritable bowel syndrome (IBS) (Walker, Middleton, and Petrowicz, 2001).

Cynara-SL (LI 120)

Choleresis (Bile Secretion)

A mode of action study using the Lichtwer product Cynara-SL (Hepar-SL) demonstrated that artichoke extract increased the flow of bile. Administration of six capsules (1.92 g) intraduodenally caused a peak increase (100 to 150 percent compared to baseline) in bile one hour later (Kirchhoff et al., 1994). According to our reviewer, Dr. David Heber, this study inferred, but did not clearly demonstrate, therapeutic benefit for dyspepsia; the one-day study was too short, was not conducted on subjects with dyspepsia, and the product was not delivered orally.

Valverde Artischocke

Hyperlipoproteinemia (Elevated Cholesterol Levels)

A study with the Novartis product Valverde Artischocke on 131 patients with elevated cholesterol (total serum cholesterol greater than 280 mg/dl) reported a 20.2 percent decrease in cholesterol, compared to 7.2 percent in the placebo group. The product was given in a dose of 900 mg, twice daily, before meals, for six weeks (Englisch et al., 2000). This well-conducted trial indicates efficacy of Valverde Artischocke in the treatment of elevated cholesterol.

POSTMARKETING SURVEILLANCE STUDIES

A review of metabolic, pharmacological, and clinical studies described two postmarketing surveillance studies (Kraft, 1997). The first study, reported by Held (1991), included 417 patients with hepatic and biliary tract disease who were treated for four weeks with artichoke leaf extract (product not named). Prior to the study, the average duration of symptoms of abdominal pain, bloating, meteorism, constipation, lack of appetite, and nausea was four months. Elimination of these symptoms occurred in 65 to 77 percent of patients after one week, and in 52 to 82 percent of patients after four weeks.

The second postmarketing surveillance study was published by Fintelmann (1996) and Fintelmann and Menssen (1996). It included 553 subjects with dyspepsia who were administered the Lichtwer product Hepar-SL. The authors reported a clinically impressive and statistically significant improvement for 87 percent of patients within six weeks of treatment. In a subset of 302 patients for whom cholesterol values were routinely determined, serum cholesterol and serum triglyceride concentrations dropped significantly ($p < 0.001$). For this group of subjects, the average daily dose was approximately 1.5 g extract and treatment extended to an average of 43.5 days (six weeks) (Kraft, 1997).

Walker, Middleton, and Petrowicz (2001) reported an analysis of another patient subset with key symptoms of irritable bowel syndrome (279 in number). These patients experienced significant reductions in symptoms (71 percent) after six weeks of treatment with six capsules per day, with improvement noted within ten days. Although the initial survey by Fintelmann and Menssen (1996) did not include all the diagnostic criteria for IBS, patients were included if they had at least three of five key symptoms.

ADVERSE REACTIONS OR SIDE EFFECTS

No adverse reactions or side effects were reported in the clinical studies described. The Fintelmann (1996) postmarketing study reported that 1.3 percent of 553 subjects experienced mild reactions, such as flatulence, feeling of weakness, and hunger.

INFORMATION FROM PHARMACOPOEIAL MONOGRAPHS

Source of Published Therapeutic Monographs

German Commission E

Indications

The German Commission E approves the use of fresh or dried artichoke leaf for dyspeptic problems due to its choleretic action (Blumenthal et al., 1998).

Doses

Fresh or dried leaf: 6 g per day (Blumenthal et al., 1998)

Contraindications

The Commission E mentions the following contraindications: known allergies to artichokes and other composites and obstruction of bile ducts. It also suggests that in case of gallstones, use only after consulting with a physician (Blumenthal et al., 1998).

Adverse Reactions

The Commission E lists no known adverse reactions (Blumenthal et al., 1998).

Drug Interactions

The Commission E lists no known drug interactions (Blumenthal et al., 1998).

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DETAILS ON ARTICHOKE PRODUCTS AND CLINICAL STUDIES

Product and clinical study information is grouped in the same order as in the Summary Table. A profile on an individual product is followed by details of the clinical studies associated with that product. In some instances a clinical study, or studies, supports several products that contain the same principal ingredient(s). In these instances, those products are grouped together.

Clinical studies that follow each product, or group of products, are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Index to Artichoke Products

Product	Page
Cynara-SL™	157
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Product Profile: Cynara-SL™

Manufacturer	**Lichtwer Pharma AG, Germany**
U.S. distributor	Lichtwer Pharma U.S., Inc.
Botanical ingredient	**Artichoke leaf extract**
Extract name	**LI 120**
Quantity	320 mg
Processing	Plant to extract ratio 3.8-5:1, aqueous extract
Standardization	No information
Formulation	Capsule

Recommended dose: For regular longer-term use to help maintain a healthy liver and digestive system and to support the normal cleansing process of the liver take one to two capsules daily. For nutritional support, take one to two capsules shortly before or after eating or drinking too much. Up to six capsules may be taken per day. Effects can be noticed as soon as 30 to 60 minutes.

DSHEA structure/function: Clinically proven to help maintain a healthy liver and digestive system; clinically proven to provide fast and

effective herbal support for the digestive system when eating or drinking too much; supports the normal cleansing process of the liver.

Cautions: If taking prescription medicine, are pregnant, nursing a baby, or administering to children under the age of 12, consult a health care professional before using this product.

Other ingredients: Lactose, gelatin, magnesium stearate, silicon dioxide, talc, titanium dioxide, sodium lauryl sulphate, FD&C blue no. 1, yellow no. 5.

Comments: Sold in Europe as Hepar-SL forte®.

Source(s) of information: Kirchhoff et al., 1994; product packaging; information provided by distributor (11/2/99).

Clinical Study: Hepar-SL forte®

Extract name	LI 120
Manufacturer	Sertürner Arzneimittel GmbH, Germany (Lichtwer Pharma AG, Germany)
Indication	**Choleresis** (bile secretion)
Level of evidence	**III**
Therapeutic benefit	**MOA**

Bibliographic reference
Kirchhoff R, Beckers CH, Kirchhoff GM, Trinczek-Gartner H, Petrowicz O, Reimann HJ (1994). Increase in choleresis by means of artichoke extract. *Phytomedicine* 1: 107-115. (Also published in *Arzneimittel-Forschung/Drug Research* 1993; 40 [1]: 1-12.)

Trial design
Crossover. Eight-day pretrial period to establish case histories and clinical and laboratory parameters. One-day treatment periods were separated by an eight-day washout period.

Study duration	1 day
Dose	Single dose of 6 capsules (1.92 g artichoke extract)
Route of administration	Intraduodenal
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind

Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	20
No. of subjects completed	18
Sex	Male
Age	Mean: 26 years

Inclusion criteria
Subjects with acute or chronic metabolic disorders with previous gastroenterological and chemical examination.

Exclusion criteria
Subjects with upper abdominal problems lasting more than four weeks, intolerance of fatty foods, irregular bowel movements with changes in feces color, heavy smokers (>10 cigarettes per day), or heavy coffee drinkers (>4 cups per day). Ingestion of metabolically active drugs not permitted two weeks prior to start of test.

End points
On days of the investigation, capsule contents were dissolved in 50 ml water and administered via an intraduodenal probe. Measurement of intraduodenal bile secretion began 30 minutes after substances were administered and continued for up to four hours using multichannel probes.

Results
Increases in bile secretion in the active group were 127.3 percent after 30 minutes, 151.5 percent after 60 minutes, and 94.3 percent after 90 minutes, each in relation to the initial value. These measurements were significantly different from placebo, $p < 0.01$. The most significant increase after administration of placebo was 39.5 percent after 30 minutes. At later times of 120 and 150 minutes the volume of bile secreted under the active treatment was still significantly higher than under placebo ($p < 0.05$).

Side effects
None reported.

Authors' comments
Results indicate that artichoke extract can be recommended for the treatment of dyspepsia, especially when the cause may be attributed to dyskinesia of the bile ducts or disorder in the assimilation of fat.

Reviewer's comments
This study was flawed by the small sample size and the short duration of treatment. (0, 5)

Product Profile: Valverde Artischocke

Manufacturer	**Novartis Consumer Health GmbH, Germany**
U.S. distributor	None
Botanical ingredient	**Artichoke leaf extract**
Extract name	**CY450**
Quantity	450 mg
Processing	Plant to extract ratio 25-35:1, aqueous extract of fresh leaves
Standardization	No information
Formulation	Tablet

Source(s) of information: Englisch et al., 2000.

Clinical Study: Valverde Artischocke

Extract name	CY450
Manufacturer	Novartis Consumer Health GmbH, Germany
Indication	**Hyperlipoproteinemia** (elevated blood lipid levels)
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Englisch W, Beckers C, Unkauf M, Ruepp M, Zinserling V (2000). Efficacy of artichoke dry extract in patients with hyperlipoproteinemia. *Arzneimittel-Forschung/Drug Research* 50 (3): 260-265.

Trial design
Parallel.

Study duration	6 weeks
Dose	2 × 450 mg twice daily, before meals
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes

Placebo	Yes
Drug comparison	No
Site description	3 hospitals
No. of subjects enrolled	143
No. of subjects completed	131
Sex	Male and female
Age	35-69 years

Inclusion criteria
Patients between 18 and 70 years old with total cholesterol of >7.3 mmol/l (>280 mg/dl) in plasma or serum. During participation in the study, patients were not allowed to take other cholesterol-lowering drugs or any antibiotic treatments.

Exclusion criteria
Patients who had taken lipid-lowering drugs within two weeks of enrollment.

End points
After enrollment, patients were seen on days 7, 14, 28, and 42. At each visit, blood samples were drawn and patient conditions noted. Blood samples were tested for total cholesterol, low-density lipoprotein (LDL cholesterol), high-density lipoprotein (HDL cholesterol), triglycerides, liver enzymes (gamma-glutamyl transferase, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, and glutamate dehydrogenase), and glucose.

Results
Artichoke extract was significantly superior to placebo in decreasing total cholesterol (18.5 percent versus 8.6 percent, $p = 0.001$), LDL cholesterol (22.9 percent versus 6.3 percent, $p = 0.001$), and LDL/HDL ratio (20.2 percent versus 7.2 percent). There was a slight decrease in gamma-GT levels in both groups from baseline to end of study, with no significant difference between groups. There were no changes to glucose levels in either group.

Side effects
No drug-related adverse events.

Authors' comments
This prospective study could contribute clear evidence to recommend artichoke extract CY450 for treating hyperlipoproteinemia and, thus, prevention of atherosclerosis and coronary heart disease.

Reviewer's comments
Well-conducted and well-designed study with positive and significant results. (5, 6)