

MEDICINAL USE OF HERBS: AN INTRODUCTORY
GUIDE FOR HEALTH CARE PRACTITIONERS

by

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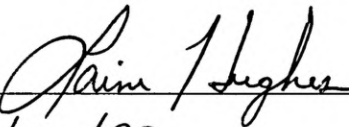
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ABSTRACT

One purpose of this professional paper was to provide a resource to assist health care practitioners in understanding U.S. regulations regarding herbal supplements and the implications of these regulations on product quality and safety. From a review of both popular and refereed literature, summaries regarding quality and safety issues were made.

Another purpose was to introduce practitioners to the medicinal use of selected herbal remedies. A review of recent clinical trials published in English on the medicinal uses of eleven selected herbs was included. This review illustrated the strengths and weaknesses of current scientific research on the safety and efficacy of selected herbs.

In this age of unprecedented herb use, health care practitioners must be open-minded, yet pragmatic about potential benefits of herbal remedies. Some herbs have certainly shown potentially promising outcomes that deserve serious consideration. Currently, however, the safety and efficacy of many herbal products remains unknown or unclear. Thus health care practitioners must continue to encourage and support sound research on herbs while proceeding with optimistic caution in the employment of herbs in medical practice.

CHAPTER 1 - INTRODUCTION

Purpose

Today's health care practitioners are increasingly faced with the responsibility for counseling patients who use herbal supplements. This responsibility may place practitioners who have received little or no formal education in the use of herbal medicine in uncomfortable predicaments. Limited availability of formal education, as well as the general paucity of scientific knowledge regarding risks and benefits of herb use, has resulted in a relative lack of knowledge concerning herbal medicine among many health care practitioners. This lack of knowledge often leads to an avoidance of the use of herbs in practice. In extreme cases, practitioners may even discourage or express hostility toward their patients who choose to use herbs (Gordon, 1996; Kent, 1997).

Despite general unfamiliarity among conventional health care practitioners about the medicinal utility of herbs, their patients continue to use herbal remedies in increasing numbers. This prevalent use of herbal remedies, however, is often undisclosed by patients as a result of their fear of repercussions from health care providers or

feelings that providers are not knowledgeable (Eisenberg et al., 1993; Eliason, Kruger, Mark, & Rasmann, 1997).

This communication barrier between patient and health care provider regarding herbs was demonstrated in a study published in the New England Journal of Medicine. This study (Eisenberg et al., 1993) revealed that 70% of respondents who acknowledged using alternative therapy reportedly never mentioned this to their primary care physician.

Gordon (1996) addressed one reason for this lack of disclosure. He stated, "patients say that physicians whom they have ordinarily found to be caring, thoughtful and understanding become angry, defensive and dismissive when the possibility of using alternative therapies is even mentioned" (p. 2209). Furthermore, others have documented claims by patients that their doctors would no longer see them if they utilized alternative modes of therapy (Kent, 1997).

The dysfunctional communication between patient and practitioner over the use of alternative therapies often threatens the vital relationship of trust that should exist. Ultimately, the ability of patients and practitioners to constructively discuss and consider all therapeutic options influences the quality of healthcare

that is delivered. Therefore, an increased understanding about herbal medicine and a reform of the conventional approach to alternative therapy is essential. Eisenberg (1997) acknowledged that health care professionals must put an end to the "don't ask, don't tell" approach to alternative therapies. An initial step in advancing alternative therapies is to develop a new approach to herbal remedies, which involves the cooperation of both health care practitioners and patients.

It is recognized by some that health care practitioners have an obligation to become more knowledgeable about the safety and efficacy of herbal medicine (Cottrell, 1996; Youngkin & Israel, 1996). As practitioners become more knowledgeable about herbal medicine, they will likely feel more comfortable and confident in addressing this form of therapy with patients. Practitioners must attempt to engage patients in dialogue regarding herbs and include inquiries about herbs in routine health histories (Eliason et al., 1997; French, 1996). The more practitioners initiate such dialogue, the more likely they are to gain their patients' trust and confidence. Subsequently, this may facilitate a more unreserved disclosure of alternative therapy use and

promote the discovery of treatment regimens that are acceptable to both patients and practitioners.

The principle aim of this professional project is to assist health care practitioners in expanding their knowledge about the medicinal use of herbs. The project will acquaint readers with elements of herbal medicine and provide guidelines for the use of selected herbs.

Background and Significance

Any casual observer of trends in modern health care would agree that the public's search for solutions to health care problems not easily remedied by conventional western medicine is ongoing. Motivation for such searching often stems from a yearning for more physically and emotionally acceptable outcomes and ultimately more effective cures. This search may also be inspired by a desire for alternatives to conventional medical practices or to gain greater independence in the choice of treatment regimens. The public's increasing reliance on herbal medicine is one example of this search for better alternatives.

Today's health care professionals should be aware of the public's increasing reliance upon herbs and strive to become more adept with herbal medicine use. The motivation

to increase one's knowledge of herbal medicine and employ this knowledge in practice begins with recognizing the prevalence of herbs in our society and understanding specific reasons for herb use. Health care professionals must also be mindful of current federal regulations and manufacturing standards governing herbal products and the implications these regulations and standards pose on safety and quality.

Prevalence of Herb Use

The need for health care practitioners to become more knowledgeable about and familiar with the use of herbal medicine is, in part, the result of widespread use of herbs by the general public. In recent years, consumer demand for herbal products and the prevalence of herb use for a variety of health and medicinal purposes is unprecedented.

A landmark study by Eisenberg et al. (1993) revealed the prevalence of unconventional therapy use in the U.S. Telephone interviews were conducted with a randomly selected national sample of 1539 adults, 18 years of age and older. Respondents were questioned about any medical conditions and about their use of conventional and unconventional therapy. Unconventional therapy was defined as medical interventions not widely taught at U.S. medical

schools or generally available at U.S. hospitals. Based on the results of this study, researchers estimated that in 1990, one in three persons in the U.S. adult population used some form of unconventional therapy. Researchers calculated that there were 425 million visits to alternative practitioners, exceeding the estimated 388 million visits to primary care physicians. Of the study's 1539 respondents, 3% had used an herbal medicine in the last year. Study conclusions estimated that \$1.2 billion was spent on dietary supplements nationwide, which includes herbal products.

Peggy Brevoort, chief executive officer of East Earth Herb Inc. in Eugene, Oregon, affirms that there is increasing demand for herbal products (Marwick, 1995). Brevoort claims that in the past 20 years, the botanical industry has grown from a few isolated companies dealing in bulk sales to a \$1.5 billion industry with an estimated annual growth of 15%.

The upward trend in use of herbal products is not just a U.S. phenomenon, similar trends are being noted worldwide. According to the Institute of Medical Statistics, the world market for nonprescription herbal medicine was worth \$11.9 billion in 1994 (De Smet & Brouwers, 1997).

A 1993 survey by the Canadian Health Monitor found that more than 20% of Canadians use some form of alternative medicine. The Canadian market for herbal products was estimated at \$150 million in 1995 (Cottrell, 1996).

In Europe, where herbal medicine is widely accepted and most extensively researched, plant-based medicines have become a substantial part of conventional drug therapy. Melville K. Eaves, business manager of Dr. Willmer Schwabe GmbH and Company in Germany stated,

In Germany, France, Italy, Austria, and Switzerland, plant drugs and phytomedicines are an integral part of conventional medicine.... There is nothing fringe or alternative in the role of phytomedicines in European health care. Many surveys in Germany, France, and other European countries show that this is what consumers want and, for that matter, what doctors want (Marwick, 1995, p. 607, 608).

Consumer Demographics

When tailoring one's practice to meet the specific needs of a particular region or population of the country, health care practitioners must know the population they serve. A desire to accommodate patients' interests in

herbal remedies thus warrants an understanding of the demographic profile of alternative therapy consumers.

Eisenberg et al. (1993) found that 38% of people 25 to 49 years of age use unconventional therapy. This was significantly higher than for those who were younger (33%) and those who were older (28%). Unconventional therapy use was significantly less common among blacks (23%) than among other racial groups (35%). Forty-four percent of respondents with some college education, in contrast to only 27% of respondents with no college education, reported using unconventional therapy. Thirty-nine percent of people earning annual incomes greater than \$35,000 were found to use unconventional therapy compared to 31% of users with lower incomes. Of persons living in the Western U.S., 44% use unconventional therapy, whereas only 31% of the rest of the country use unconventional therapy. Investigators acknowledged that representation of their sample was limited to those persons with a telephone. This limitation may have excluded some minority and indigent populations. However, they noted that their sample corresponded with that of the National Health Interview Survey with respect to age, sex, race, social class, and other sociodemographic variables (Eisenberg et al., 1993).

Reasons for Herb Use

Essential background information for any discussion of herbal medicine must include reasons for the public's use of herbs and their motivation for seeking alternative medicine in general. Gordon (1996) declared that,

The vast majority of people who seek out alternative therapies have, or believe they have, explored the utility of conventional western approaches. Most have chronic illnesses...for which western medicine can usually offer only symptomatic relief or palliation, not definitive treatment.

Eliason et al. (1997) surveyed 136 patrons of two health food stores in the metropolitan Milwaukee area. The most common reasons for respondents' use of dietary supplements in this study included good health and general illness prevention, cardiovascular benefits, gastrointestinal benefits, musculoskeletal problems, and energy and metabolism.

Eliason et al. (1996) interviewed patients from a family practice clinic in suburban Milwaukee. Of the 200 respondents, 53% reported taking dietary supplements. Respondents' reasons for using supplements were similar to the study cited above and included nutrition and energy

enhancement (29%) and cancer prevention or immune enhancement (24%).

Although not specifically targeting herbs but rather alternative health care among family practice patients, Elder, Gillcrist, and Minz (1997) discovered that 30% of their study's respondents were using herbal medicine. Cited reasons for using alternative therapy were similar to those above, but a large percentage was for illness and injury prevention (30%) and wellness (44%). In using alternative therapy, authors of this study claim that patients may be seeking more control over their health, expressing frustration with western medicine, or simply seeking another treatment modality.

De Smet (1993) noted several characteristics of consumers of alternative medicine. His findings demonstrated that these consumers have less faith in conventional medicine, believe that one can build up resistance to disease, have a chronic illness showing poor response to conventional medicine, desire more control over their own health care, and feel that alternative health care providers are more patient-oriented.

Practitioners' Lack of Formal Education

Traditionally, herbal medicine has received little attention in the U.S. education process (French, 1996). Schools of pharmacy, for example, have typically not offered courses on the use of herbal remedies or they de-emphasized pharmacognosy or the science of natural drugs altogether ("Herbal Roulette," 1995; Tyler, 1996).

In response to growing consumer demands for herbal medicines and patients' desires for health care providers who are knowledgeable in their use, formal education in the U.S. is attempting to make some changes. A recent study by Wetzel, Eisenberg, and Kaptchuk (1998) revealed that U.S. medical schools are beginning to adjust their curricula in order to provide students with some introduction to alternative therapies. In this study, all 125 U.S. medical schools were surveyed. Of the 117 schools that responded, 64% reported offering one or more courses in complimentary or alternative therapy or at least included these topics in required courses.

Although at a slower pace, curricula in nurse practitioner programs are also evolving to accommodate the need to prepare health care providers with some background in alternative therapies. A national survey of 240 nurse

practitioner tracks was conducted to assess the prevalence of instruction in complimentary therapy. Of the 118 programs that responded, 36% reported the inclusion in their curricula of planned learning experiences in complementary therapy (Hahn, 1997).

Despite these curriculum changes, the availability of formal education on herbal medicine in the U.S. remains limited. In addition to limited formal education, scientific research on the safety and efficacy of herbs is not abundant. Eliason et al. (1997) noted that most of the research on herb efficacy has been performed in Europe and Asia. They claim that U.S. physicians are less familiar with this research and consequently have a limited understanding concerning the possible application of herbs in the treatment of a variety of conditions.

Another factor contributing to the lack of scientific research in the U.S. relates to patent protection. Recent estimates place the cost of developing a new compound for drug use at \$231 million over 12 years. Most of this cost accrues in the testing for safety and efficacy that is required for FDA approval (Tyler, 1993). Tyler noted that the maximum 17-year patent protection for pharmaceuticals begins when a drug is in the early stages of development. By the time pharmaceuticals are approved by the FDA, about

90% of these have less than 11 years of patent protection remaining. He stated, "the old 'plant' drugs, some of which have been known and used for centuries, do not even qualify for this degree of protection" (p. 12).

Consequently, unless there are indications that they will be able to recover the costs of development and show a profit, the pharmaceutical industry and most manufacturers of herbal products are not willing to invest in studies on the safety and efficacy of herbs.

In 1978, Germany established an expert panel of physicians, pharmacists, pharmacologists, toxicologists, epidemiologists and other professionals familiar with the scientific body of literature on herbs and medicinal plants. This panel, known as Commission E, has reviewed the safety and effectiveness of over 300 herbs and publishes its results in monograph form in the *Bundesanzeiger*, the German equivalent of the U.S. Federal Register. According to Tyler (1993), these monographs make up the most current and useful information on the safety and efficacy of plant drugs. Unfortunately, the German Commission E monographs were not available in English until August of 1998. Therefore, this valuable source of scientific information on herbal medicine has largely been

unavailable to U.S. health care professionals until recently.

Public's Sources for Information

Scarce scientific research on herb safety and efficacy, combined with health care practitioners' limited knowledge regarding medicinal uses of herbs, have contributed to the public's search for information from other sources. Two studies by Eliason et al. (1996, 1997) found that respondents frequently use herbal supplements based on their own knowledge or on information obtained from family, friends, and the media.

Unfortunately, such information is often incorrect, misleading, and even harmful. Cottrell (1996) noted sales promotions for botanical products as one example of possible misinformation. There is often a fine line between pure information and sales pitch in many of these promotions. Some retailers provide pamphlets detailing the uses for herbal products but typically provide little or no supporting scientific evidence to back their claims. One example is the well-known herb, Mistletoe. Mistletoe is commonly purported by popular writers as a curative agent for cancer (Tyler, 1993). Sales in Germany of a monopreparation of Mistletoe, categorized as a cancer

treatment, totaled 18 million in U.S. dollars in 1996. Despite its popularity, the fact that eludes much of the public is that there is no scientific documentation of mistletoe's efficacy for treating cancer. Due to a lack of scientific evidence, the German Commission E does not recommend any therapeutic application for Mistletoe (Blementhal et al., 1998).

Regulations & Manufacturing Standards

Essential to responsible patient counseling regarding herb use is an understanding of current federal regulations and manufacturing standards. A brief overview of these regulations and standards follows.

Prior to the 1962 amendment to the Federal Food, Drug, and Cosmetic Act of 1938, herbs were considered drugs (Youngkin & Israel, 1996). The 1962 amendment made it requisite that all drugs undergo extensive, research-laden scrutiny to be proven safe and effective. Without this proof, a drug could not be marketed as such (Tyler, 1996).

Although producers of herbal products have supplied the Food and Drug Administration (FDA) with the necessary data for drug approval on a few herbs, mostly laxatives, they have not done so for the majority of herbs. To avoid the previously mentioned estimates for time and costs of

developing a new drug, manufacturers began marketing herbs as foods or food supplements (Tyler, 1996).

Without claiming therapeutic utility, which was unlawful for unapproved drugs, herb marketers and health food stores used creative labeling and a vast array of literature to promote the effectiveness of herbal products in treating specific diseases (French, 1996). This advertising, however, was often meant to promote sales rather than candidly inform. In the wake of perceived false advertisement and misinformation, FDA commissioner David A. Kessler threatened to remove herbal products from the market. Public outcry over this threat lead Congress to pass the Dietary Supplement Health and Education Act of 1994 (Tyler, 1996).

The Dietary Supplement Health and Education Act of 1994 (DSHEA) is the foundation of current federal regulations on herbal products and other dietary supplements. A thorough review and discussion of DSHEA will elucidate the law's implications for herbal product manufacturing, labeling, marketing, quality, and safety. This review and discussion is included in chapter 2.

Quality and Safety

In addition to awareness of current regulations and manufacturing standards on herb quality and safety, health care practitioners should understand the inherent dangers and possible adverse effects of some herbs. Like most pharmaceutical products, there are associated risks with herb use. Health care practitioners are more likely than consumers to understand this fact and thus have a responsibility to inform their patients and the public about potential dangers.

A common phenomenon resulting from the public's misinformation and misunderstanding about herbs is their tendency to equate natural with safe. Unfortunately, there is no inherent safety in many natural substances (Chan, 1997; Marwick, 1995). As one author phrased it, "snake venom is natural but deadly" (Eisenberg, 1997, p. 62). Although many herbs are completely safe and often effective for the treatment of a variety of conditions, others are very toxic and unfit for human use. Issues surrounding the potential adverse effects resulting from the ingestion of impurities or an inherently toxic herb deserve thorough discussion and are explored further in chapter 2.

Objectives

Owing to the lack of formal education and the paucity of scientific knowledge on herbal medicine, this project is an attempt to introduce health care practitioners to the medicinal use of herbs. This project is intended to be an introduction to herbal medicine and thus invites readers to further inquiry and investigation of other resources.

The primary objective of this project is to synthesize information gleaned from a review of regulations and manufacturing standards, general safety and quality, and randomized clinical trials on selected herbs. This information will form the foundation of proposed guidelines and recommendations for the safe and effective use of 11 selected herbs, which comprises chapter 4 and Appendix D. Specific information not yielded by the above review, such as daily dosages, use in pregnancy, drug interactions, etc. have been drawn from reputable sources such as the German Commission E Monographs and other publications.

A review of current U.S. regulations and manufacturing standards will focus primarily on the Dietary Supplement Health and Education Act of 1994. Manufacturing and marketing practices that have evolved from this legislation will be explored. Literature concerning the general

quality and safety of herbal products has been surveyed. Practical guidelines for purchasing and using herbal products based on this literature are proposed. Randomized clinical trials on 11 selected herbs have been summarized to better understand the scientific rationale for their medicinal use. These 11 herbs were selected on the basis of their perceived relevance to and potential usefulness in primary care settings and also on the availability of randomized clinical trials published in English. The herbs included in this project are St. John's Wort, Garlic, Valerian, Peppermint, Cranberry, Echinacea, Capsicum, Ginger, Feverfew, Ginkgo biloba, and Saw palmetto.

CHAPTER 2 - LITERATURE REVIEW

Introduction

A literature review of current laws and regulations governing dietary supplements is included in the following discussion. Inherent quality and safety issues associated with these laws and regulations are discussed. The most recent and available clinical research published in English on selected herbs is also reviewed here.

Regulations and Manufacturing Standards

Since most herbs are not required to meet the strict regulations to which drugs are subjected in the U.S., practitioners must be cautious and pragmatic in their approach to herbal therapy. An awareness of the implications of current laws and regulations governing herbal supplements is an essential first step to such an approach. The following discussion focuses on the Dietary Supplement Health and Education Act of 1994 and the resultant manufacturing standards on herbal products.

Dietary Supplement Health
and Education Act of 1994

Following an overhaul of the regulations governing U.S. food labels in 1993, the FDA turned its attention toward

renovating dietary supplement labels as well. In response to the FDA's call for stricter regulations and to FDA Commissioner David A. Kessler's threat to remove herbal products from the market entirely, Congress was inundated with protest mail from millions of concerned consumers (Herbal Roulette, 1995; Tyler, 1996).

Pressured by threats of bold maneuvers by the FDA on one side and public outcry on the other, Congress was compelled to draft new legislation regarding dietary supplement regulation. The subsequent passage of the Dietary Supplement Health and Education Act of 1994 (DSHEA) was an attempt by Congress to appease the FDA's demands for safe and appropriately labeled herbal products. At the same time, they wanted to reassure consumers and manufacturers that herbal products would remain available for those who choose to use them (Dietary Supplement, 1995).

Aside from the assurance that dietary supplements would remain on the market, DSHEA's passage represented a small victory for consumers and manufacturers. This victory came in the form of Congress' acknowledgment of a link between the ingestion of certain dietary supplements and better health and disease prevention. Despite their vow to take swift action against adulterated and unsafe

products, Congress reassured consumers and manufacturers that they would not enact legislation impeding Americans from improving their health through the free choice of safe dietary supplements. In other words, dietary supplements, including herbal products, would remain in the marketplace (Dietary Supplement, 1994).

The new law emphasizes that dietary supplements are neither food additives nor drugs. The definition of a dietary supplement includes a substance that contains one or more of the following ingredients: a vitamin, mineral, herb or other botanical, or an amino acid. A dietary supplement can also be a concentrate, metabolite, constituent, or extract of any of these ingredients (Dietary Supplement, 1994).

So long as no medicinal or direct drug effect is claimed on the product label, a dietary supplement is not categorized as a pharmaceutical and thus avoids subjection to the strict, research-laden testing that drugs undergo (Chan, 1997). As a result, almost any substance not claiming drug effects can be marketed as a dietary supplement without first being required to demonstrate either safety or effectiveness (Eliason et al., 1997).

If there are questions about a product's safety or effectiveness, the burden to prove the product unsafe lies

with the FDA, not the product's manufacturer. Only if the FDA discovers that a product's ingredients present "substantial or unreasonable risk of illness or injury" is the supplement branded as adulterated and removed from the market (Dietary Supplement, 1994).

Despite being restricted from making medicinal or direct drug claims, a supplement label may describe how the product effects the so called "structure and function" of the body or the "well-being" achieved through its use or consumption. In order to make these claims, manufacturers must have substantiation (yet to be defined by the FDA) that they are truthful and not misleading. However, unless the FDA challenges a product's claims, manufacturers are not required to show this substantiation. The only disclaimer required of the manufacturer is a statement on the product label that the FDA has not evaluated or approved the claims and that the product is not intended to diagnose, treat, cure, or prevent any disease (Dietary Supplement, 1995; Herbal Roulette, 1995).

A label must identify the product as a dietary supplement and include the name and quantity of each ingredient or the total quantity of all ingredients in a proprietary blend. Unless covered by a specific U.S. compendium (e.g., U.S. Pharmacopeia, Homeopathic

Pharmacopeia of the United States, or the National Formulary) the supplement must be the product identified on the label and contain the strength it is represented to have. Furthermore, all herbal product labels must specify the part of the plant from which the ingredients were derived (Dietary Supplement, 1995).

DSHEA established the Commission on Dietary Supplement Labels. This Commission is composed of 7 members, who have expertise and experience in manufacturing, regulation, distribution, and use of dietary supplements. The Commission's main objective is to determine how best to provide truthful and scientifically valid information to the public in order to help them make the most informed choices regarding supplement use (Dietary Supplement, 1994).

The Office of Dietary Supplements at the National Institute of Health was also created as a requirement of DSHEA. Its purpose is to promote scientific research on dietary supplements with the intent to more fully explore the utility of dietary supplements in maintaining and improving health and in preventing chronic disease (Dietary Supplement, 1994).

DSHEA does not apply directly to advertising. However, it has generated questions about the Federal Trade

Commission's (FTC) approach to dietary supplements.

Although the FDA and Federal Trade Commission (FTC) work closely together, the FDA has primary responsibility for product labeling of dietary supplements and the FTC is responsible for dietary supplement advertising claims. FTC policy has formerly mandated that dietary supplement advertising be truthful, not misleading, and substantiated. In 1998, however, the FTC has for the first time issued advertising guidelines aimed specifically at dietary supplements (Grady, 1998).

Whereas FDA labeling rules forbid manufacturers from making claims that supplements treat or prevent disease, the FTC allows advertisements to make such claims, so long as they provide substantiation. Substantiation has been defined as reliable tests, analyses, and research that is conducted and evaluated by qualified professionals. Information provided for substantiation must represent the totality of evidence and not simply those findings that support the supplement's claims. The FTC also requires that advertisements include qualifying information such as side effects and whether a person who endorses the product is being compensated or is qualified to make the endorsement. Advertisements may not claim that the supplement has been approved by the FDA, which, as

discussed earlier, has no authority to regulate a supplement unless it violates labeling rules or is implicated in consumer harm or illness (Grady, 1998).

Manufacturing Standards

Under DSHEA, the FDA was granted the authority to establish "good manufacturing practices" (GMPs) for dietary supplements. In cooperation with manufacturers and interested public, the FDA intends to establish GMPs that govern the preparation and packing of supplement products (Dietary Supplement, 1995). However, specific manufacturing standards have yet to be instituted by the FDA. A 1995 source claimed that it would be at least two years before any federal manufacturing standards were introduced (Herbal Roulette, 1995). In a workshop on herbal medicine at the University of Utah in May 1998, Constance J. Geiger, PhD, RD, reaffirmed that there are still no federal regulations that mandate specific manufacturing standards for herbal products (Geiger, 1998).

On one side, manufacturers enjoy free reign to market herbal products without first demonstrating their safety and efficacy. On the other side, in the case of a complaint or suspicion regarding a product's safety or efficacy, the FDA is burdened with the responsibility to

investigate these complaints. This precarious relationship between manufacturers and the FDA, in combination with ambiguous manufacturing standards, has created loopholes vulnerable to exploitation. Unfortunately, such exploitation has led to adulterations in herbal products, which have often lead to potentially disastrous outcomes.

Herbal product adulterations have included the variability of active ingredients from brand to brand or within like products of the same manufacturer. These products are also frequently misidentified by importers and domestic manufacturers alike and are subsequently mislabeled. In addition, herbal products often contain ingredients that are not on the product label and are sometimes void of the professed active ingredient entirely. Furthermore, ingredients have been found to exist in forms that the body cannot use or that are inherently toxic (Herbal Roulette, 1995; Marwick, 1995; Miller, 1996; Pittenger, 1997).

A Consumer Reports' study analyzed ten different brands of ginseng for the amount of ginsenoside, the purported active ingredient. The study found that the amount of ginsenoside varied greatly among all ten brands and had no correlation with the milligram amount of ginseng that was printed on the label (Herbal Roulette, 1995).

Other studies reveal inconsistent quality in supplement products. In 1995, the Center for Science in the Public Interest reported its results on tests of several brands of garlic pills. The report indicated that allicin, the purported active ingredient for lowering cholesterol, varied more than 40-fold among brands. The National Organization for Rare Disorders evaluated 12 brands of L-carnitine and found that 2 brands contained no detectable carnitine. Other brands varied in their amount of carnitine from 20% to 85% of the labeled quantity (Herbal Roulette, 1995).

In 1994, the Lancet published a study of 50 ginseng products sold in 11 countries. Out of 50 products, 6 contained no specific ginsenosides. One of the ginseng preparations that was void of ginsenosides, contained a large amount of ephedrine (Cui, Garle, Eneroth, & Bjorkhem, 1994).

Anderson (1996) listed three cases of gross adulterations of herbal products. The first was found in Cow's Head brand of an oriental herb known as Tung Shueh. Chemical analysis revealed that each tablet contained diazepam, indomethacin, mefenamic acid, and diclofenac. Of these ingredients, diazepam and mefenamic acid were not listed on the label. Another adulteration was discovered

in the Chinese herb, *Jin Bu Huan*. Tablets of this herb were found to contain a potent analgesic levo-tetrahydropalmatine, which is derived from the genus *Stephania*. The plant of origin listed on the label, however, was the genus *Polygala*, which is promoted for use as an expectorant and sedative. The third adulteration involved the Chinese herb *Stephania tetrandra* and *Magnolia officinalis*. Chemical analysis of 12 samples of this product revealed contamination with aristolochic acid, which is derived from the potentially nephrotoxic herb, *Aristolochia fangchi*.

Quality and Safety

Documented adulterations bring attention to the need for clearer and more specific standards governing the manufacturing of herbal products. Until the FDA institutes such standards, however, users of herbal products must actively pursue reliable information and proceed cautiously in order to avoid potential hazards.

Purchasing and Utilization

Responsibly informing oneself involves an awareness of fundamental principles regarding purchasing and utilizing herbal products. However, health care practitioners who

counsel patients on herb use should emphasize that despite efforts to be informed and to give responsible advice, such advice will remain imperfect and a matter of judgment as long as efficacy and safety cannot be assured (Eisenberg, 1997).

Through a review of the professional literature, some practical approaches and common sense guidelines to purchasing and utilizing herbal products were discovered. Each item in this list of guidelines (see Appendix A) may have specific relevance to patient, health care practitioner, or both. Although an adherence to these recommendations does not guarantee avoidance of potential adverse outcomes, mindfulness of them may help one to utilize herbal remedies more safely.

Herbs Considered Unsafe

As previously mentioned, responsible and appropriate precautions with the use of herbal remedies does not necessarily preclude one from experiencing untoward effects. Despite the all too popular notion that natural substances are essentially healthy and safe, there are some herbs that are inherently toxic and should be avoided.

The literature is replete with examples of adverse effects resulting from the ingestion of herbal products. A

familiar and relatively recent case study involved a 60-year-old woman who developed hepatitis following the daily use of chaparral capsules for 10 months. The woman's hospital course was complicated and she underwent orthotopic liver transplantation as well as cadaveric renal transplantation. More than 1½ years after the liver transplant, liver chemistries finally reached normal limits and the patient was relatively well (Gordon, Rosenthal, Hart, Sirota, & Baker, 1995).

Although an extreme example, the above case emphasizes the point that herbal remedies are not free of risks and can sometimes be extremely dangerous. In addition to being familiar with herbs that are relatively safe and effective, health care practitioners should acknowledge the existence of toxic herbs as well. When approached by patients with questions regarding herbal supplements, the ability to identify potentially harmful herbs will be invaluable. It is beyond the scope of this project to identify every toxic or harmful herb, but some relatively common herbs that have shown potentially harmful effects have been identified (see Appendix B).

Review of Clinical Trials of Selected Herbs

Despite concerns over the general quality and safety of herbal products, many herbal remedies have a place in the treatment of a variety of physical and emotional ailments. Historical proof of the therapeutic utility of herbal remedies, however, is often based on hypothetical and anecdotal evidence. Although such evidence has merit, research-based science in the safe and effective use of herbal remedies is the gold standard for establishing confidence for clinical use. Although herb research is still in its infancy, many well-designed clinical trials have been conducted to test the medicinal value of herbs. The following is a review of some of the most current scientific studies on the medicinal utility of selected herbs. This review is limited to studies or analyses published in English, however, which excludes the majority of scientific research from Europe.

St. John's Wort

Hypericum perforatum, also known as St. John's Wort, is a perennial herb native to Europe and Asia and introduced to the U.S. by European colonists. The name St. John's Wort was derived from the fact that it flowers around St. John the Baptist's Day (June 24). Traditionally, St.

John's Wort has been used for a wide variety of conditions including inflammation, sedation, analgesia, diuresis, and malaria. More recently, the herb has become popular for its use in depression (Miller, 1998). Although much of the activity of St. John's Wort has been attributed to the ingredient hypericin, Tyler (1993) noted that recent studies have linked this herb's antidepressant activities to the presence of various xanthenes and flavonoids, which may act as monoamine oxidase (MAO) inhibitors. However, according to the Commission E monograph on St. John's Wort, the demonstrated MAO activity is either nil or very slight (Blementhal et al., 1998).

Hansgen, Vesper, and Ploch (1994) conducted a 6-week, randomized, double-blinded trial to compare the effectiveness of hypericum extract LI 160 to a placebo in the treatment of major depression. Sixty-seven patients from 11 neurology, psychiatry, and general practices participated in the study. Inclusion criteria included: age 18 to 70 years, met the criteria for major depression according to the DSM-III-R, scored 16 or more on the Hamilton Depression Scale (HAMD), and had a depressive episode for a minimum of 2 weeks and a maximum of 6 months. The treatment group received 900 mg of hypericum extract daily, while the control group received a placebo.

Participants were monitored at 0, 2, 4, and 6 weeks with the following psychometric tests: HAMD, depression scale of von Zerssen (D-S), complaint inventory (BEB), and Clinical Global Impression index (CGI).

Compared with the placebo group, all four psychometric tests revealed statistically significant improvements in the treatment group following four weeks of therapy. The placebo group subsequently experienced similar improvement after being switched to LI 160 during the fifth and sixth weeks. No notable side effects were observed in either group. Although all participants knew that they would receive the trial medication for at least two weeks, it is important to note that the placebo group experienced no real improvement in symptoms until receiving LI 160 during the final two weeks (Hansgen et al., 1994).

A study by Wheatley (1997) compared the effects of LI 160 to amitriptyline in treating mildly to moderately depressed outpatients. The study was a 6-week, randomized, double-blinded, multicenter trial. Subjects were between the ages of 20 and 65 years, had a current major depressive episode according to DSM-IV criteria, and scored between 17 and 24 on the HAMD. One group (N = 83) was given 900 mg of LI 160 daily and the other group (N = 73) received 75 mg of amitriptyline daily. Patients were evaluated six times

throughout the study using the HAMD, Montgomery-Asberg Rating Scale for Depression (MADRS), and the CGI. Routine hematology and biochemistry screens were done on visits 1 and 6, as well as assessments for adverse events at visits 3 through 6.

Superior efficacy in reducing HAMD and MADRS scores was demonstrated by the amitriptyline group. However, no significant differences between the two groups were noted in the primary outcome measure (i.e., total HAMD score of less than 10 at the end of the study or a reduction from baseline of at least 50%) and the secondary outcome variable (GCI). Furthermore, LI 160 was found to be far more tolerable than amitriptyline in terms of side effects. Of the LI 160 group, 37% complained of adverse effects compared to 64% in the amitriptyline group. No differences in laboratory data were noted between the two groups. A major limitation of this study was that 75 mg of amitriptyline is only half the maximally recommended dosage. Also, information about possible adverse events specifically associated with tricyclic antidepressant, which were apparently given to both treatment and control groups, may have biased the number of adverse effects seen in the LI 160 group (Wheatley, 1997).

Vorbach, Arnoldt, and Hubner (1997) compared the efficacy of LI 160 to imipramine in the treatment of severely depressed patients in a randomized, double-blinded, multicenter, 6-week trial. Persons between the ages of 18 and 70 years, who had a severe episode of major depression according to the ICD-10, were admitted to the study. One group (N = 107) received 1800 mg of LI 160 daily and the other group (N = 102) received 150 mg of imipramine. On days -3, 0, 7, 14, 28, and 42, patients were evaluated with the HAMD, CGI, and D-S psychometric instruments and received a clinical examination, as well as laboratory tests, blood pressure and heart rate assessment. Adverse events were recorded on five different occasions throughout the study.

Except for a slight trend in favor of imipramine on the CGI, differences in measured responses to LI 160 and imipramine were negligible. In terms of safety and tolerability, there were no differences between the two groups in laboratory values, blood pressure, or heart rate. The percentage of reported adverse effects was notably higher in the imipramine group (41%) compared to the LI 160 group (23%). The authors conclude that LI 160 was almost as effective as imipramine, but with the major advantage of having significantly less pronounced adverse effects,

particularly dry mouth, diaphoresis, GI symptoms, and constipation (Vorbach et al., 1997).

Linde et al. (1996) published a meta-analysis of 23 randomized or quasi-randomized, controlled, clinical trials on the effectiveness of St. John's Wort in the treatment of mild to moderately severe depression. The most consistently used instruments to measure treatment effects were the HAMD scale and CGI index. The analysis indicated significantly superior effects of hypericum extracts (daily dosages of 300-900 mg) over placebo and similar effectiveness compared to standard antidepressants. The percentage of adverse effects was significantly lower in patients on hypericum (19.8%) compared to those on standard antidepressants (52.8%). This report is limited, however, by the fact that many trials in the analysis were published more than once without mention of prior publication, the classification of depression was not uniform and sometimes vague, and not every trial used the same preparation of hypericum. Moreover, daily dosages of hypericum extract, and thus the amount of hypericin, were inconsistent (Linde et al., 1996).

Many of the St. John's Wort studies reviewed above tested daily dosages of 900 mg of hypericum extract vs. a placebo or a tricyclic antidepressant. All of these

studies demonstrated that 900 mg of hypericum extract had superior efficacy over placebo and similar effectiveness compared to tricyclic antidepressants. Most of the studies, however, used only half or less than half of the maximum daily dosage of a given tricyclic antidepressant. Maximum dosages may have produced significant improvement over hypericum extract. All studies reported either no adverse effects from St. John's Wort or significantly fewer side effects than tricyclic antidepressants.

Garlic

Garlic (*Allium sativum*) has been used for a variety of mythical purposes such as warding off vampires and witches and in treating a number of medical diseases such as cancer and tuberculosis. Garlic contains the sulfur-containing amino acid derivative, alliin. When in contact with the enzyme alliinase, which occurs when garlic bulbs are ground, alliin is converted to allicin, a reportedly potent antibacterial agent. Garlic also contains a self-condensation product of allicin known as ajoene. Ajoene is known to inhibit platelet aggregation, which is believed to provide protection from atherosclerosis and thrombosis (Tyler, 1993). Recently garlic has been the focus of serious clinical research due to its potential benefits in

reducing the risks of cardiovascular disease. The principle aim of this review is to analyze garlic's effects on serum lipids and to a lesser extent on blood pressure.

A randomized, double-blinded, controlled trial to evaluate the cholesterol-lowering effects of garlic was conducted by Berthold, Sudhop, and Bergmann (1998). Subjects had moderate hypercholesterolemia (240-348 mg/dL). None of the participants had taken lipid-lowering drugs in the past 8 weeks and all were advised to abstain from other dietary supplements and adhere to their usual diet. A cross-over design was used so that one group received 12 weeks of garlic, followed by a 4-week washout period, and then 12 weeks of a matching placebo. The other group received a placebo-garlic sequence. Treatment groups were given a preparation containing 5 mg of steam-distilled garlic oil in a daily dosage equivalent to 4-5 g of fresh garlic.

Twenty-five subjects completed the trial. The garlic preparation was well tolerated with the exception of a few cases of garlic odor and slight abdominal discomfort. Despite similarities in macronutrient intake in both phases of the study and consistent body weights over the entire course of treatment in all subjects, serum lipoprotein

concentrations remained essentially unchanged between placebo and garlic treatment (Berthold et al., 1998).

A study, similar in purpose to the above trial, was conducted to evaluate the effects of garlic powder tablets on plasma lipids and lipoproteins, as well as their tolerability (Isaacsohn et al., 1998). This was a double-blinded, placebo-controlled, parallel group design. After 4 weeks of diet stabilization, participants who demonstrated a mean LDL cholesterol level of 160 mg/dL or lower and a triglyceride level of 350 mg/dL or lower on two of four visits were admitted to the study. Fifty subjects were randomized to treatment with either garlic powder tablets (Kwai®) 300 mg 3 times daily or identical placebo for 12 weeks. The garlic dosage was equivalent to 2.7 g of fresh garlic per day.

Following completion of the 12-week trial, baseline blood pressure, heart rate, and body mass index did not change significantly between the two groups. Furthermore, no statistically significant changes were detected in any of the specified lipid, lipoprotein, or apolipoprotein parameters. Adverse effects among subjects in the garlic treatment group included complaints of garlic breath (3), descriptions of a change in body odor (2), abdominal discomfort (2), and one case of intestinal obstruction.

The investigators viewed the intestinal obstruction to be unrelated to the trial drug (Isaacsohn et al., 1998).

Kwai garlic powder tablets were tested in another study to assess their effects on serum lipids and lipoproteins, glucose, and blood pressure (Jain, Vargas, Gotzkowsky, & McMahon, 1993). The 12-week trial was randomized, double-blinded, and placebo controlled. Subjects were required to have a serum total cholesterol of greater than or equal to 220 mg/dL. Subjects were restricted from taking any lipid-lowering agents for at least one month prior to the start of the study and each participant was advised to make no changes in diet or physical activity during the 12-week trial. Forty-two participants were randomized either to a treatment group that received 300 mg garlic tablets 3 times daily or to a placebo group that received a matching placebo tablet 3 times daily. A lipid profile, serum glucose, blood pressure, heart rate, and body weight were assessed at baseline, 6 weeks and 12 weeks.

Garlic tablets were well tolerated by participants. No significant odor problems were noted and only 1 out of 20 patients in the treatment group complained of increased eructation. At the end of the 12-week trial, total cholesterol levels were lowered by 6% in the treatment

group and 1% in the placebo group. The decrease in total cholesterol was primarily the result of lowered LDL cholesterol, which decreased 11% during the course of the trial. A small but insignificant rise in triglycerides was seen in both groups. No significant changes were noted in HDL cholesterol, serum glucose, blood pressure, or body weight. The results of this study may be limited due to a slightly lower mean age in the treatment group (7 years), as well as a lower percentage of smokers, 55% in the treatment group compared to 90% in the placebo group (Jain et al., 1993)

Warshafsky, Kamer, and Sivak (1993) published a meta-analysis on studies that tested the effects of oral garlic preparations on total cholesterol levels. Five studies met the inclusion criteria of being published, randomized, and placebo-controlled, and tested subjects with serum cholesterol levels exceeding 200 mg/dL. Four of the five studies were double-blinded and all five used a parallel group design. No dietary restrictions were placed on participants. A total of 365 participants completed the trials; 184 were randomized to treatment groups and 181 to placebo groups. Type of garlic preparation and dosage varied among trials. Three trials used Kwai powder; one

used spray-dried powder, and another used an aqueous extract. Daily dosages ranged from 600 to 900 mg.

The above analysis showed that total serum cholesterol levels were lowered by 9% among treatment groups. The authors concede, however, that the quality of the studies was not optimal. None of studies reported how subjects were recruited; only two studies reported enzymatic methods of cholesterol analysis; no trial addressed how the placebo was similar in taste and smell to the garlic preparation; and none of the trials assessed dietary intake, weight, or exogenous garlic intake (Warshafsky et al., 1993).

Garlic's potential cardiovascular benefits also relate to claims that it has the ability to lower blood pressure. A majority of studies of garlic's effects on blood pressure were done in Germany. One meta-analysis, however, is available in English and was conducted by Silagy and Neil (1994). The analysis included 8 randomized, controlled trials, which tested the effects of garlic powder tablets on blood pressure. The trials included data from 415 subjects. All trials used Kwai garlic powder but with varying daily dosages of 600-900 mg, equivalent to 1.8-2.7 g/day of fresh garlic. Duration of therapy ranged from 4 weeks to 10 months with a mean of 12 weeks.

Seven of the 8 trials compared garlic's effects on blood pressure with that of a placebo. Three of the seven found significant reductions in blood pressure in the participants treated with garlic. Compared to placebo groups, participants in treatment groups experienced an average decrease in systolic blood pressure of 7.7 mm Hg and an average decrease in diastolic pressure of 5.0 mm Hg. Among garlic-treated subjects, the incidence of experiencing garlic odor was 7.7%. Significant increases in other side effects were not reported. The authors concluded that a standardized garlic powder preparation of 600-900 mg/day appears to lower blood pressure over 1 to 3 months. However, the authors also cautioned readers about the limitation of these studies due to generally poor quality assessment measures (i.e., no reports of techniques to achieve randomization, no attempts to assess compliance with therapy, no use of automated devices or random-zero sphygmomanometers to measure blood pressure (Silagy & Neil, 1994)).

Clinical trials on garlic reported contradictory findings. Of the two studies considered the most well designed, neither demonstrated garlic's effectiveness at lowering serum lipid levels. Another study exhibited a 6% drop in LDL cholesterol, but also found a concurrent small

increase in triglycerides and no change in HDL cholesterol. Furthermore, this later study was flawed in that the treatment group and the placebo group were far from homogenous. Indications that garlic may have some clinical use in treating mild hypertension, as demonstrated by a meta-analysis of 8 clinical trials, are overshadowed by the inconsistent quality of the study designs.

Most garlic studies in this review used daily dosages equivalent to 1.8 to 2.7 g of fresh garlic. One study used an equivalent of 4 to 5 g of fresh garlic per day. Side effects from Garlic use were few and included garlic odor, abdominal discomfort, and increased eructation.

Valerian

Valerian is a perennial plant found in temperate regions of North America, Europe, and Asia. Common valerian or *Valeriana officinalis* is the most widely cultivated form for medicinal use (Leathwood, Chauffard, Heck, & Munoz-Box, 1982). Valerian has been valued for more than 1000 years as an effective tranquilizer and calmative. Valerian root contains essential oil with monoterpenes and sesquiterpenes valerenic acid or valeranone, but none has been proven to have central nervous system depressant properties (Tyler, 1993).

Despite its unknown mechanism of action, valerian's potential effects to improve sleep are of interest here.

A 1994 study by Schulz, Stolz, and Miller tested valerian's effects on objective and subjective measures of sleep. The study was a double-blinded, placebo-controlled, parallel-group design. Subjects included 14 elderly females who were measured to be poor sleepers by inclusion criteria. Eight subjects were randomized to the treatment group and six to the placebo group. Quality of sleep was measured by polysomnography (EEG, EOG, EMG, and ECG) during three nights at 1-week intervals (N0, N1, and N2).

Questionnaires were given to assess subjective sleep quality. Subjects in the treatment group were given 405 mg of Valdispert® forte tablets (each tablet contained 135 mg of valerian extract). A loading dose of 3 tablets was given one hour before polygraphic sleep recordings on the second laboratory night (N1). Thereafter, each subject took Valdispert forte, 450mg three times daily for the next seven days prior to the third and final laboratory night (N2).

Participants in the valerian group experienced an increase in slow-wave sleep (sum of sleep stages 3 and 4) and a decrease in sleep stage 1. REM sleep remained unchanged. Significant changes in participants' subjective

sleep patterns were not noted. This study was limited by a small test group and lack of homogeneity between the treatment and placebo groups (i.e., baseline sleep period time was greater and sleep latency time shorter in the placebo group) (Schulz et al., 1994).

Twenty-seven consecutive patients from a medical clinic, who reported fatigue and sleep difficulties, were recruited for a double-blinded crossover study of a valerian preparation, Valerina Natt. The trial drug, which contained 400 mg of valerian root, 375 mg of *Flores humuli*, and 160 mg of *Lemon melissa*, was compared to an identical extract with the exception of containing only 4 mg of valerian root. Subjects were told that the study was testing which valerian preparation was more effective. Subjects were randomized as to which preparation they would receive on the first night, after which the other preparation would be given on the second night. All participants rated their quality of sleep on the second morning (Lindahl & Lindwall, 1989).

The test preparation was rated better than the control by 21 of the 27 subjects. Reporting on sleep quality, 24 of 27 subjects stated they experienced improved sleep from the test preparation and 44% reported perfect sleep. Participants reported no side effects. Small test groups,

short test duration, and lack of objective measures of outcome limit the results of this study.

An older but frequently cited study in the literature is a clinical trial comparing the effects on sleep of an aqueous extract of valerian, a commercial preparation of valerian, and a placebo (Leathwood et al., 1982). The extract contained 400 mg of valerian and the commercial preparation (Hova®) contained 60 mg of valerian and 30 mg of hop flower. The valerian extract, commercial preparation, and placebo were all sealed into identical Parke-Davis snap-fit capsules. Participants (128 volunteers) were presented 9 sachets in random order; each contained 3 valerian extract, 3 Hova, and 3 placebo. Participants took one sachet of pills on 9 nonconsecutive nights and after each night completed a post-sleep questionnaire. Instructions were given to avoid taking the pills on evenings followings excessive food intake, drinking, or exercise.

The results of this study revealed that valerian extract significantly decreased subjectively reported sleep latency scores. A significant improvement in subjectively rated sleep quality was also seen, particularly among subjects who considered themselves poor or irregular sleepers or to have long sleep latencies and also among

subjects who smoked. The valerian extract had relatively no effect on night awakenings, dream recall, or feelings of somnolence on the morning after taking the drug. On the other hand, the only change produced by the Hova preparation was a significant increase in subjective reports of feeling more sleepy in the morning after taking the preparation (Leathwood et al., 1982). Again, short test duration and the lack of any objective measurements of outcome warrant caution in interpreting the results of this study. The post-sleep questionnaire used to measure subjectively reported sleep quality was chosen on the basis of a pilot test, which showed that this type of questionnaire was the most acceptable. No discussion of the tool's validity is given, however.

The same valerian extract used in the above study was tested at two different dosages in 18 healthy young subjects sleeping either at home or in a sleep laboratory (Balderer & Borbely, 1985). Sleep quality was based on subjective questionnaires, night-time motor activity, and sleep EEG. Ten subjects with a mean age of 32.5 years were monitored at home. Monitoring consisted of questionnaires and self-rating scales as well as a recording of night-time motor activity. Participants in the home group were given 450 mg of valerian extract, 900 mg of valerian extract, or

placebo on Wednesday or Thursday night of 3 consecutive weeks in a double-blinded, crossover design. Subjects were instructed to avoid napping and alcohol or caffeine consumption prior to each test night. The laboratory group, which consisted of 8 subjects with a mean age of 22.6, were given similar instruction but were under different test conditions. Differences included staying one adaptation night in the laboratory prior to testing, receiving only the 900 mg valerian dose or placebo, receiving 3 days of placebo and one day of valerian in different sequences for 2 weeks, and being monitored with polygraphic sleep recordings and an all-night spectra analysis of sleep EEG.

Under home conditions, a 50% reduction in subjectively rated sleep latency and wake time after sleep onset was noted after taking the 900 mg dosage of valerian. The 450 mg dosage had only a slightly smaller effect. With higher valerian dosages, an observation of slight enhancement in motor activity during the middle third of the night as opposed to reduced activity in the last third suggested a dose-dependent effect (Balderer & Borbely, 1985).

In the laboratory, none of the measured parameters differed significantly between valerian nights and placebo nights. However, both subjective and objective

measurements of sleep latency and wake time after sleep onset were lower on valerian nights compared to placebo nights, demonstrating a trend toward the observation made under home conditions (Balderer & Borbely, 1985). Small test groups and short test duration limit the findings of this study and warrant cautious interpretation.

Overall, the above valerian studies were of marginal quality. Outcomes, however, were fairly consistent. Two studies tested 400-900 mg of valerian extract and another tested 135 mg. The fourth study tested 400 mg of valerian root. All of the studies involved very small test groups and a short test duration. All studies tested subjectively rated sleep quality, two of which included no objective measurements. Except for one study of 135 mg of valerian, each study reported a significant improvement in subjectively reported sleep quality. Those with objective measures found either no change or modest improvement in tested parameters. One study's participants reported no side effects. The other three studies made no mention of side effects.

Peppermint

Mentha piperita (peppermint) of the Lamiaceae family is a hybrid cross that sprouted from a field of spearmint in

England in 1696. Although it has been cultivated primarily for its fragrant volatile oil, peppermint has been used for medicinal purposes as well. Peppermint's volatile oil, which contains menthyl acetate, menthol, and menthone, is believed to contain properties effective in treating indigestion, flatulence, colic, and irritable colon (Blementhal et al., 1998; Tyler, 1993).

One study tested the effects of an enteric-coated peppermint preparation (Colpermin®) on 110 Chinese outpatients with active symptoms of irritable bowel syndrome (i.e., intermittent, colicky abdominal pain, distension, and altered bowel habits) (Liu, Chen, Yeh, Huang, & Poon, 1997). The trial was conducted as a double-blinded, placebo-controlled, parallel group design. Subjects were randomly assigned to receive either Colpermin or a placebo, one capsule three to four times daily 15-30 minutes before meals for 4 weeks. Each Colpermin capsule contained 187 mg of peppermint oil in a thixotropic gel to ensure adequate dispersal in the bowel. Placebos were identical capsules containing an inert oil. Subjects documented the severity of symptoms on entry into the study and after two and four weeks of treatment. Side effects were documented and liver function tests were done before

treatment and again at 1 and 3 months after completion of the study.

Subjects treated with Colpermin showed statistically significant improvement in irritable bowel syndrome (IBS) symptoms compared to those in the placebo group.

Improvement in symptoms usually occurred within 2 weeks of treatment and then stabilized. Among the treatment group, 79% experienced alleviation of abdominal pain, 83% reported less abdominal distension, 83% had reduced stool frequency, 73% experienced less borborygmi, and 79% reported less flatulence. However, no changes in nausea, acid regurgitation, eructation, or heartburn were noted in the treatment group. One patient in the treatment group experienced heartburn due to chewing the capsules rather than swallowing them and another developed a mild skin rash over both forearms. No significant changes in liver function tests were seen, even among subjects who chose to continue treatment 1-2 months after the designated 4-week treatment phase (Liu et al., 1997).

An earlier trial conducted by Schneider and Otten (1990) also tested the effects of Colpermin on patients with IBS. The trial design was double-blinded and placebo-controlled. Two groups of 30 subjects each were randomized to receive either Colpermin or placebo for 2 episodes of 6

weeks in a crossover fashion, which included a 2-week washout period before each treatment phase. In addition to a daily diary of pain and bowel movements, subjects self-evaluated their pain, bowel movements, transit time, accompanying symptoms, and general well being at 3, 6, 9, and 12 weeks (Schneider & Otten, 1990).

This study found no significant differences between Colpermin and placebo in defecation frequency or consistency in relation to symptoms recorded in daily diaries. After three weeks of therapy, however, the treatment group reported significant improvement in pain. Furthermore, at 3 and 6 weeks the Colpermin group claimed that their general well being had improved and that they had fewer episodes of pain per week. The only reported adverse effect was an occasional perianal burning sensation (Schneider & Otten, 1990). Aside from gender and a diagnosis of IBS, a description of this study's participants is not mentioned. A description of the evaluation methods or measurement tools is lacking. Furthermore, the authors failed to mention the exact dosage of peppermint given to the treatment group.

Dew, Evans, and Rhodes (1984) conducted a double-blinded, crossover design, multicenter trial to test the effects of peppermint oil in IBS. Six males and 23 females

with a mean age of 42 years participated in the study. All participants had typical symptoms of IBS. The treatment group received peppermint oil gelatin capsules coated with cellulose acetate phthalate to ensure content release into the distal intestine. The placebo group received identical looking placebo capsules filled with arachis oil; caps of the placebo containers were injected with peppermint oil to ensure that the aroma was similar to the treatment containers. Depending on the severity of symptoms, subjects took between 3 and 6 capsules daily for each treatment period of two weeks. Each day during the treatment period, subjects recorded abdominal symptoms, stool frequency, side effects, and overall symptoms.

Subjects in this study indicated feeling significantly improved while taking peppermint oil capsules compared with placebo and stated that peppermint oil was better than placebo in relieving abdominal symptoms. There was no difference in the effect on daily bowel actions between treatment and placebo groups (Dew et al., 1984). The study failed to mention whether any side effects were experienced. It is unknown whether subjects were randomized and what dosages of peppermint were used in the treatment capsules.

Characterized by motility disturbances with bloating, diffuse abdominal pain, nausea, vomiting, and intolerance to certain foods, non-ulcer dyspepsia is frequently associated with IBS. A 4-week, placebo-controlled, double-blinded, parallel group study was carried out to test the efficacy and safety of a combination preparation of peppermint oil and caraway oil (Enteroplant®) in 45 patients with non-ulcer dyspepsia (May, Kuntz, Kieser, & Kohler, 1996). Subjects were randomized to a treatment group and a control group. Both groups were homogenous with respect to intensity of pain and severity of the disorder. Each group received a 4-week regimen of 3 capsules daily of either treatment or placebo. The treatment medication consisted of Enteroplant enteric-coated capsules containing 90 mg of peppermint oil and 50 mg of caraway oil. The patients' general physical condition, subjective ratings of pain intensity and frequency, medical prognosis, and Clinical Global Impressions (CGI) scores (items 1-3) were assessed at 2 weeks and at the end of treatment. Adverse effects from drug therapy were also recorded.

At the end of the 4-week treatment phase, both target parameters (i.e., pain intensity and CGI scores) were significantly improved in the treatment group as compared

to the placebo group. Whereas all subjects in the treatment group complained of moderate to severe pain before the start of treatment, 63.2% of these patients were reportedly pain free by the end of the study. Furthermore, of those treated with the peppermint/caraway oil, pain symptoms had improved in 89.5% and CGI scores had improved in 94.5%. There were a total of 7 adverse events among all participants (4 treatment, 3 placebo). Among the treatment group, these were substernal burning with severe eructation and nausea, flatulence and increasing acid taste, hyperventilation, and suspected grand mal with syncope (May et al., 1996).

Peppermint trials reviewed above are of mixed quality. Two of the four appear to have relatively sound designs, whereas the other two do not provide enough information to accurately critique them. Both of the latter failed to specify the exact peppermint dosage tested in the treatment group and their methods were either poorly described or not discussed. The two studies that did specify treatment dosages used daily doses of 270 to 561 mg of peppermint oil. All four studies were consistent in their findings of improved abdominal pain. Two studies were congruous in finding no change in the frequency or consistency of bowel

actions. Side effects were minimal, the most frequent being heartburn and perianal burning.

Cranberry

Cranberry (*Vaccinium macrocarpon*) has long been valued for its pleasant acidulous flavor and is found in numerous juices, sauces, relishes, and jellies. In addition to its value in foods, cranberry is believed to be helpful in preventing and treating recurrent urinary tract infections. Since the early part of this century, researchers have attempted to identify the antibacterial properties of cranberry. Though earlier studies were inconclusive and often contradictory, many believed that cranberry's antibacterial effects stemmed from its ability to acidify the urine. More recent research, however, discounts these earlier notions and proposes an entirely different mechanism of inhibition of microorganism adherence to the epithelial cells that line the urinary tract, particularly *E. coli* (Tyler, 1993).

E. coli is potentially uropathogenic due to the presence of two adhesins on its hair-like fimbriae that allow it to cling to epithelial cells in the urinary tract. Ofek et al. (1991) discovered that cranberry juice contains two substances that inhibit *E. coli* adhesins. One of these

substances is fructose. The other is a polymeric compound of unknown nature. Out of seven juices tested (blueberry, cranberry, grapefruit, guava, mango, orange, and pineapple), only cranberry and blueberry juice contained this second polymeric compound.

A 6-month study of the effects of cranberry juice on bacteriuria and pyuria was conducted in 1994 by Avorn et al. (1994). This trial was randomized, double-blinded, and placebo-controlled. Participants included 153 elderly women who were recruited from a multilevel long-term care facility for the elderly, as well as from nine housing complexes for elderly residents. Subjects were randomized to either a standardized, commercially available cranberry juice cocktail or to an indistinguishable placebo beverage. The treatment and placebo groups were similar in the occurrence of bacteriuria, pyuria, and urinary tract symptoms at baseline, but the treatment group had a lower rate of urinary tract infections by history. All cranberry juice samples were tested and found to inhibit *E. coli* adhesion in vitro, whereas none of the placebo samples exhibited anti-adhesive properties. Subjects were instructed to consume 300 ml daily in single or divided doses and to avoid consuming any other cranberry products. This study included all subjects who were able to produce a

baseline urine sample and at least one other sample after randomization, but most subjects' urine was tested on a monthly basis for six months. Standard urinalysis, culture, and sensitivities were performed immediately after collection.

The incidence of bacteriuria and pyuria in urine samples collected from the treatment group was 15% compared to 28.1% in the placebo group. The average 1-month probability of converting from infected to non-infected urine was 54% in the treatment group as opposed to 28% in the control group. On the contrary, the average 1-month probability of converting from non-infected to infected urine was 9% in the cranberry group compared to 12% in the placebo group. Therefore, cranberry's ability to both cure and prevent UTIs was apparently better than placebo. A blinded physician initiated treatment for UTIs in 16 control group subjects compared to 8 treatment group subjects. The study found no significant difference between the two groups in the acidification of urine.

Another group of researchers conducted a study to examine the role of cranberry in preventing the recurrence of urinary tract infections among younger women (Walker, Barney, Mickelsen, Walton, & Mickelsen, 1997). This clinical trial was a double-blinded, placebo-controlled,

crossover design. Subjects were generally healthy with the exception of a history of recurrent urinary tract infections (4 UTIs in the previous year or at least one UTI within the previous 3 months). Only 10 subjects completed the 6-month trial, 6 subjects in one group and 4 in the other. To ensure a consistent entry point and before initiating the study, each participant was precluded from beginning the study until they developed a UTI. This initial UTI was treated with a 10-day course of antibiotic. Thereafter, each participant received either cranberry or placebo for two 3-month periods. The treatment consisted of a daily dose of 400 mg of cranberry solids. Laboratory tests demonstrated significant in vitro *E. coli* anti-adherence activity of the cranberry preparation. Both the cranberry solids and placebo were encapsulated in identical opaque capsules. Subject were interviewed monthly regarding compliance and incidence of side effects. Participants were also instructed to report urinary tract symptoms to the attending physician. After confirmation of an infection, subjects received treatment with antibiotics while maintaining adherence to either the cranberry or placebo regimen.

While taking cranberry vs. placebo, 7 of the 10 subjects demonstrated fewer UTIs. In the remaining

subjects, 2 experienced the same number of UTIs and 1 experienced more. Out of a total of 21 UTIs that occurred during the 6-month trial, only 6 occurred while subjects were taking cranberry (Walker et al., 1997). Although the methodology was generally sound, these results are limited by small test group sizes.

The two cranberry studies above tested daily dosages of 300 ml of cranberry juice or 400 mg of cranberry solids. Results consistently demonstrated that cranberry was effective in reducing the incidence of UTIs. Neither study mentioned any adverse effects from cranberry ingestion. Extremely small treatment and placebo groups limit the validity of one study.

Echinacea

Also known as the purple coneflower, echinacea is a native American wildflower of the daisy family. There are 9 species of echinacea native to the central United States. The species most often utilized today is *Echinacea purpurea*. Native Americans first introduced the value of echinacea to a German physician of Pawnee City, Nebraska (Tyler, 1993). Echinacea is a purported remedy for more ailments than any other plant (Hobbs, 1994; Tyler, 1993). The most reliably documented claims of echinacea, however,

are its immune-modulating effects (i.e., increased number of white blood cells and spleen cells and increased phagocytic activity of granulocytes). A particular active ingredient responsible for these effects has yet to be determined (Blumenthal, 1998; Tyler, 1993).

Two German studies, frequently cited in the literature, comprised a large portion of the scientific evidence for the use of echinacea that was presented at an herbal medicine conference at the University of Utah in spring 1998. The first by Braunig, Dorn, and Knick (1992) was a placebo-controlled, double-blinded trial of *Echinacea purpurea* root extract in 180 patients with the flu. Three groups were assigned to receive one of three regimens: echinacea 900 mg/day, echinacea 450 mg/day, or placebo (55% ethanol, 45% water, and sugar coloring). The study found that the 450 mg/day regimen was no more effective than placebo in reducing the severity or duration of flu-like symptoms. However, a statistically significant improvement in the severity and duration of flu-like symptoms was found in those treated with the 900 mg/day dosage (Hobbs, 1994; Shane-McWhorter, 1998).

In the second study, echinacea was tested in 108 volunteers who had chronic upper respiratory tract infections (Schoneberger, 1992). Half of the sample was

given 2-4 ml/day of a liquid echinacea preparation (Echinacin®) for 8 weeks and the other received placebo for the same period of time. Compared to 25.9% of the placebo group, 35.2% of the echinacea group stayed healthy through the course of treatment. The echinacea group also experienced longer illness free periods as opposed to the placebo group (i.e., 40 days between colds vs. 25 days). In addition, 78% of the echinacea group who contracted an infection had less severe symptoms and recovered more quickly. Whether the differences between treatment and control groups were statistically significant was not mentioned (Foster, 1994, Shane-McWhorter, 1998).

Between 1984 and 1992, a group of researchers performed 5 studies on the safety and immunomodulating effects of 4 echinacea preparations (Melchart et al., 1995). Study 1 and 5 tested an intravenous homeopathic preparation of *E. angustifolia* (.4 ml IV once daily for 5 days and 10 mg IV once daily for 4 days respectively). Study 2 and 3a tested an oral extract of *E. purpurea* root (333 mg and 380 mg by mouth three times daily for 5 days). Study 3b tested an extract of *E. pallida* root (dosage not specified). And study 4 tested an extract of *E. purpurea* herb (800-900 mg by mouth daily for 5 days). All studies were randomized and placebo-controlled, and all but one

were double-blinded. A total of 134 subjects participated in the studies; each was a healthy volunteer between the age of 18 and 40 years. None of the participants had experienced an acute infection or taken any immunomodulating drugs in the two weeks prior to the start of each study. Observation periods ranged from 9 to 14 days. The primary outcome measures for immunomodulating activity was the relative phagocytic activity of polymorphonuclear neutrophil granulocytes (PNG), measured with a microscopic method in studies 1 and 2 and with a cytometric method in the studies 3, 4, and 5. The secondary outcome measure was the number of leukocytes in peripheral venous blood. Safety was assessed by 6 to 8 periodic laboratory tests on blood samples, as well as monitoring temperature, blood pressure, and heart rate. In addition, participants kept a record of all subjective side effects.

Treatment groups in studies 1 and 2 exhibited significantly enhanced phagocytic activity of PNGs compared with placebo groups, while in the other studies no significant effects were observed. No change in leukocyte numbers was noted in any of the 5 studies. Each echinacea preparation was well tolerated and no side effects were detected. The authors concede that the results are

difficult to interpret due to the relatively small sample sizes within each study, the various test preparations used, and the different methods employed to measure immunomodulatory activity (Melchart et al., 1995).

A study was conducted to assess the ability of *Echinacea purpurea* extract to stimulate the cellular immune function of peripheral blood mononuclear cells (PBMC) in normal individuals and in persons with AIDS and chronic fatigue syndrome (CFS). Peripheral blood mononuclear cells, in the presence or absence of *E. purpurea*, were tested for natural killer (NK) cell activity versus K562 cells and antibody-dependent cellular cytotoxicity (ADCC) against human herpesvirus 6 infected H9 cells. Subjects included 20 healthy individuals, 20 patients with CFS, and 20 patients with AIDS. During the course of the study, participants were not allowed to use any agent known to have immunomodulating effects. Both NK cell and ADCC activity were assessed by standardized assays (See, Broumand, Sahl, & Tilles, 1997).

Significant enhancement of NK-cell function was seen when concentrations of echinacea ≥ 0.1 $\mu\text{g/ml}$ were present with PBMCs from each of the three test groups. Furthermore, ADCC activity against herpesvirus 6 was also

significantly increased in all three groups when the same echinacea concentration was present (See et al., 1997).

Echinacea studies reviewed here are very difficult to compare and interpret. *E. purpurea* was the most commonly tested species but several oral and intravenous preparations were used. Dosages were often unclear or not specified and ranged from fractions of milliliters and micrograms to varied milligram dosages. The most consistent oral dosages were between the 900 and 1140 mg per day. In addition, one study investigated the in vitro action of a liquid extract of *E. purpurea*, which is difficult to directly compare with in vivo studies. Most studies, however, consistently reported some form of immunomodulating enhancement. Side effects were either not found or not mentioned by the authors.

Capsicum

Capsicum, also referred to as cayenne pepper, chili pepper, or red pepper, consists of the dried fruit of *Capsicum frutescens*, *Capsicum annum*, or a number of hybrids. Of interest here is the compound capsaicin, a principle constituent of capsicum (Tyler, 1993). Capsaicin has been shown to deplete and prevent the reaccumulation of substance P (primary neurotransmitter of painful stimuli)

from local sensory nerve terminals (Virus & Gebhart, 1979). Recent scientific study has focused on the utility of capsaicin in treating a variety of painful conditions, which have responded poorly to conventional therapy.

Scheffler, Sheitel, and Lipton (1991) tested the efficacy of a topical 0.075% capsaicin cream (Axsain®) in 49 patients with peripheral polyneuropathy secondary to diabetes. This was a double-blinded, placebo-controlled trial. Patients were randomly assigned to treatment with either capsaicin or a vehicle cream, applied to painful areas 4 times daily for 8 weeks. No changes in any currently used oral medication were made, and the addition of any new oral analgesic, anti-inflammatory, or CNS-acting drug was prohibited. In addition, other topically applied medications being used to treat the condition were discontinued 7 days prior to the start of the study. Efficacy of treatment, as well as compliance and the occurrence of side effects, was assessed at 2-week intervals through the course of treatment. Pain was assessed by a visual analog scale (VAS) and by the physicians' global evaluation scale (PGE). Patients also rated the effect on pain associated with several daily activities including sleep, walking, working, participating in recreation, wearing shoes and socks, and eating.

The capsaicin and placebo groups were comparable in age, sex, race, type and duration of diabetes, and duration of neuropathy. After eight weeks of treatment, the capsaicin group exhibited statistically significant improvement over the placebo group in pain status measured by PGEs, 89.5% vs. 50%. The percentage of change in pain intensity, as well as the mean pain relief, as measured by the VAS was also statistically significant at week 8 for the capsaicin group vs. placebo group. Participants in the capsaicin group also recorded statistically significant improvement in sleeping and walking. Although not statistically significant, effects on other daily activities also showed clinical improvement. No serious adverse events were recorded. The most frequent side effect, experienced by 61% of the treatment group, was a burning sensation at the site of application. This event occurred most often in the first two weeks of treatment and diminished with continued use for most patients (Scheffler et al., 1991).

A second study measuring the efficacy of capsaicin in patients with diabetic neuropathy was conducted by a collective body of researchers known as the Capsaicin Study Group ("Effects of Treatment," 1992). Its methods and design were identical to those of the above study, with the

exception of a larger number of participants. In this study 277 diabetic patients were randomly assigned to capsaicin therapy or placebo.

Among the treatment and control groups, there were no statistically significant differences in demographics, type and duration of diabetes and neuropathy, severity of pain at baseline, and pretreatment functional capacities. Compared with control, the capsaicin group exhibited statistically significant improvement in functional ability to work, walk, and participate in recreational activities. Improvements in the ability to wear shoes and socks were reported in both groups. According to PGEs, 71.3% of the capsaicin group showed improvement compared with 51.3% of the control group. Furthermore, the VAS measured a statistically significant difference between capsaicin and placebo group in the mean percentage decrease in pain intensity at the end of eight weeks of treatment. Similar to the above study, the most frequently reported side effect was a burning sensation at the site of application (63% in the capsaicin group and 17% in the placebo group). This side effect was reported by 39% of the capsaicin group at the end of the study, suggesting a tolerance or diminished effect with continued treatment. Because a burning sensation is related to its therapeutic benefit,

the investigators acknowledged that finding a perfect placebo may be impossible, thus limiting their ability to maintain an ideal blinded study ("Effects of Treatment," 1992).

Deal et al., (1991) conducted a double-blinded, placebo-controlled, multicenter trial on the effects of 0.025% capsaicin cream in patients with osteoarthritis (OA) and rheumatoid arthritis (RA). Ninety-three patients, 29 with RA and 64 with OA, completed the 4-week study. Patients were randomized to treatment with either capsaicin cream or placebo, applied 4 times daily to both sides of an affected knee. Patients were not allowed to change or add to their currently prescribed oral medication. Other topical medications or corticosteroid injections were prohibited seven days prior to beginning the study and throughout its 4-week duration. At weeks 1, 2, and 4, patients were assessed for the effects of treatment on the occurrence of side effects. A VAS and PGEs were used to assess patients' response to treatment.

Following four weeks of treatment, PGE results showed a statistically significant decrease in knee pain among the capsaicin group compared to placebo. Patients with osteoarthritis exhibited a 33% mean decrease in pain and patients with rheumatoid arthritis exhibited a 57% mean

decrease. In addition, reductions in knee pain measured by VAS were also statistically superior for those treated with capsaicin vs. placebo. Burning at the site of application (mostly mild and transient) was experienced by 44% of the treatment group and by one individual in the placebo group. Suspecting that the high percentage of burning reactions may compromise blinding, the researchers performed an additional two-tailed analysis of PGEs, comparing the difference in treatment effects among the capsaicin-treated subjects who experienced burning and those who did not. No differences in treatment outcome were found among these two groups (Deal et al., 1991).

The utility of capsaicin in the treatment of arthritis was studied further by McCarthy and McCarty (1992). This double-blinded, placebo controlled trial tested the efficacy of 0.075% capsaicin cream in 21 patients with either RA or OA of the hands. Patients were randomized to treatment with either capsaicin or placebo, applied to affected hand joints 4 times daily for four weeks. All antirheumatic drugs and treatments were allowed to continue as long as no changes were made during the four weeks of treatment. Intraarticular steroid injections or topically applied agents other than capsaicin or placebo were prohibited for at least three weeks prior to the start and

through the end of the study. In addition to assessment for adverse events, outcome measures were assessed at weeks 1, 2, and 4. A categorical scale and VAS measured pain severity; morning stiffness was recorded by the Lansbury 2 question method; a Health Assessment Questionnaire (HAQ) estimated functional capacity; grip strength was assessed by a standard sphygmomanometry method; joint swelling was measured with a jeweler's tape; and tenderness was assessed with a calibrated dolorimeter.

Among OA patients using capsaicin, tenderness scores and pain assessments increasingly improved and reached statistical significance compared to placebo group by the fourth week of therapy. No trends in favor of capsaicin were noted, however, in swelling, grip strength, morning tenderness, subjective pain assessed by a categorical scale, and function as measured by HAQ (McCarthy & McCarty, 1992). Moreover, RA patients in the capsaicin group did not experience improvement in any of the measured parameters listed above. Local burning at the application site was the only adverse event noted, and was in fact recorded by every subject in the capsaicin group. Consistent with findings of other studies, the burning became less after the first week of treatment and was increasingly tolerable by the end of the trial. Again, the

authors acknowledged the difficulty of maintaining true double-blinding due to local burning experienced by all members of the treatment group. They also recognized the potential for obtaining different results, particularly among patients with RA, if a larger group had been tested (McCarthy & McCarty, 1992).

Watson et al. (1993) tested the efficacy of capsaicin in treating postherpetic neuralgia (PHN). This study consisted of a 6-week, double-blinded, placebo-controlled trial. This was immediately followed by a continuation of the original study to test the long-term (up to two years) safety and efficacy of capsaicin use. The only difference in the long-term phase of the study was that subjects and investigators remained blinded to their previous treatment, however, all subjects in the long-term phase were treated with capsaicin. A total of 125 patients completed the 6-week phase and 83 of these volunteered to participate in the long-term phase as well. Patients were at least 18 years old and had experienced PHN for six months duration or longer. No changes or additions to patients' current medications were allowed. All topical medications were discontinued seven days prior to the start of the trial through the end of the 6-week phase. Patients were randomized to treatment with either 0.075% capsaicin cream

or to an identical-appearing placebo, applied to painful areas 4 times daily for six weeks. After two, four, and six weeks of therapy, efficacy was assessed by functional capacity, PGEs, and VAS. With the exception of functional capacity, the same parameters were measured in the long-term phase at two and four weeks and every eight weeks thereafter.

During the 6-week phase, the capsaicin group experienced significant improvement in all efficacy parameters at nearly all time points throughout the study. In contrast, efficacy parameters remained essentially unchanged for subjects treated with the vehicle placebo. Furthermore, the benefits demonstrated in the 6-week phase were either maintained or improved in 86% of subjects who completed the long-term phase of the study. During the initial six weeks, 60% of patients treated with capsaicin experienced burning, stinging, or erythema at the application site, mostly during the first week of treatment. Throughout the long-term phase, only 7 of the 83 participants reported burning or stinging, suggesting that this side effect either diminished or disappeared over the course of treatment (Watson et al., 1993).

Zhang and Li Wan Po (1994) conducted a meta-analysis of 14 randomized, double-blinded, placebo-controlled trials

on the efficacy of capsaicin cream (0.025% or 0.075% cream applied 4 times daily) in the treatment of diabetic neuropathy, osteoarthritis, post-herpetic neuralgia, psoriasis, and post-mastectomy pain. Of four trials in patients with diabetic neuropathy, all exhibited trends in favor of capsaicin, although only two reached statistical significance. Three trials conducted on osteoarthritis patients were analyzed. Only one of three reached statistical significance, but all three were in favor of the utility of capsaicin. Rheumatoid arthritis was also investigated in two of these trials, one showing favorable results and the other demonstrating no benefit. Data from only one trial in patients with PHN was reported; patients exhibited improvement with capsaicin use after six weeks. The analysis included four trials on capsaicin use in psoriasis. Each of the trials reported improvement, particularly in severity of itching, scaling, and erythema. A single study in post-mastectomy patients reported favorable results in controlling jabbing pain and providing overall pain relief.

The above studies on capsaicin cream exhibit strong evidence in favor of its efficacy in relieving the pain of diabetic neuropathy, arthritis, postherpetic neuralgia, psoriasis, and post-mastectomy pain. The dosage tested in

each of these studies was either 0.025% or 0.075% cream applied to painful areas 4 times daily. Each study is relatively sound in design and showed consistent improvement in pain relief according to a visual analogue scale and physician's global evaluation scale. The most common side effect, which was found in a majority of treatment group subjects in each study, was a burning sensation at the site of application. All studies reported that this sensation diminished or disappeared with continued use. Most authors recognized the link between capsaicin's burning sensation and its therapeutic effect, and thus acknowledged the difficulty of maintaining true double-blindedness.

Ginger

The rhizome (underground stem) of *Zingiber officinale*, or ginger, is believed to possess beneficial effects as a digestive aid, stimulant, diuretic, and antiemetic (Tyler, 1993). Touted actions also include positive inotropy, enhanced saliva, gastric juice, and bile secretion, and increased peristalsis (Blumenthal et al., 1988). The majority of scientific research in the U.S. has investigated the antiemetic potential of ginger. Antiemetic effects are believed to result from local action

in the stomach, not to any central nervous system activity (Tyler, 1993).

A randomized, double-blinded, placebo controlled trial investigated the efficacy of ginger in postoperative nausea and vomiting (Arfeen et al., 1995). Subjects included 108 women between the ages of 18 and 75 who underwent elective gynecological laparoscopic surgery. Subjects were randomly assigned to receive one of three preoperative regimens: two placebo tablets (cellulose-microcrystalline), one placebo and one 500 mg ginger capsule, or two 500 mg ginger capsules. Both ginger and placebo were encapsulated in opaque black capsules. Ginger or placebo was taken with a routine preoperative dose of diazepam 10 mg one hour before the induction of anaesthesia. No antiemetics were given intraoperatively. At three hours postoperatively, investigators determined whether patients had experienced nausea, vomiting, and/or any side effects.

The overall occurrence of postoperative nausea and vomiting in this study was 31% and 20% respectively. Although not statistically significant, the incidence of nausea and vomiting increased proportionately with larger doses of ginger. Among 72 subjects who received ginger, 4 experienced side effects. Side effects included flatulence, bloated feeling, heartburn, nausea, and

eructation. The authors concluded that doses of 0.5 g and 1.0 g of ginger are ineffective in preventing postoperative nausea and vomiting (Arfeen et al., 1995). Ginger's potential interaction with concomitantly administered diazepam was not addressed.

Similar to the above study, Phillips, Ruggier, and Hutchinson (1993) investigated the antiemetic effects of ginger in 120 gynecological patients over the age of 16 receiving elective laparoscopic surgery. Patients were randomly assigned to treatment with either 10 mg of metoclopramide, 1 g of powdered ginger root, or 1 g of lactose (placebo). All capsules were indistinguishable in color, size, taste, and smell. Capsules were swallowed one hour before the induction of anaesthesia; no other preoperative medications were given. Efficacy and safety were assessed at discharge from recovery, at discharge from the hospital, and again at 24 hours following surgery. Patients were evaluated for the occurrence of nausea and/or vomiting, as well as any adverse effects.

After randomization, all three treatment groups were comparable with regard to demographics, duration of preoperative fasting, duration of surgical procedure, indication for surgery, and reports of previous postoperative nausea and vomiting. The incidence of

postoperative nausea and vomiting was 21% in the ginger group, 27% in the metoclopramide group, and 41% in the placebo group. The requirement for postoperative antiemetics was also lower among the ginger group (15%) than the metoclopramide group (32%) and the placebo group (38%). Specific adverse effects were not mentioned, but the authors stated that the incidence of adverse side effects were very low and did not differ between groups (Phillips et al., 1993).

Ginger's effects on motion sickness and gastric function were compared to that of scopolamine and a placebo (Stewart, Wood, Wood, & Mims, 1991). Twenty-eight volunteers between the age of 18 and 40 participated in the study. Motion sickness was assessed using the "stair case protocol". This protocol tested susceptibility to motion sickness in subjects who were blindfolded and placed in a chair that rotated at increasing velocities up to 35 rpm or until subjects reached a specified score on the Graybiel scale of motion sickness symptoms. Another protocol to test motion sickness employed simultaneous visual and vestibular stimuli. Gastric function was determined by gastric emptying measured by nuclear medicine techniques and also by gastric electrical activity monitored with a cutaneous electrogastrogram (EGG). Participants were

either randomly assigned to treatment or assigned using a "Latin square" design.

Eight participants in the motion sickness study were assigned to receive treatment with 500 mg or 1000 mg of ground ginger root, 0.6 mg of scopolamine, or placebo. One hour after ingesting ginger or placebo and 30 minutes after ingesting scopolamine, motion sickness susceptibility was evaluated using the staircase test. Eight additional subjects were given either 1000 mg of fresh ginger or placebo and tested in a similar fashion.

Participants who were subjected to visual and vestibular stimuli ($N = 4$) were assigned to treatment with 940 mg of ginger or placebo. In these subjects, motion sickness susceptibility was tested 15 minutes after ingesting either ginger or placebo.

Eight subjects participated in the gastric function part of the study. After subjects ingested either 500 mg of ginger or placebo, gastric function was assessed under normal circumstances or immediately following induced motion sickness using the staircase protocol describes above.

In the motion sickness study, scopolamine was found to be statistically superior to ginger. Under normal conditions, no change in gastric emptying was noted between

ginger and placebo. Following induced motion sickness, gastric emptying was noticeably slowed but no changes were observed between ginger and placebo treated subjects. In motion sickness, ginger partially inhibited EGG activity but did not enhance EGG amplitude. Gastric burning, which may have been associated with supine positioning, was reported by three of eight subjects who participated in the gastric emptying test. Also an intense urge to urinate approximately 30 minutes after ingesting ginger was reported by two subjects (Stewart et al., 1991). This study was limited by extremely small test groups. Furthermore, there is no mention as to whether investigators or subjects were blinded to treatment.

A study frequently cited in the literature investigated the efficacy of ginger in suppressing gastrointestinal symptoms associated with motion sickness. Mowrey and Clayson (1982) compared powdered ginger to dimenhydrinate in 36 volunteers who reported increased susceptibility to motion sickness. Twenty to 25 minutes before being subjected to a motorized revolving chair used to induce motion sickness, participants were given 100 mg of dimenhydrinate, 940 mg of powdered ginger, or placebo. Every 15 seconds during the test duration, investigators would record the magnitude of motion sickness determined by

a psychophysical method (geometric means of estimating the magnitude of gastrointestinal sensation from subjective ratings of stomach feeling intensity). The experiment was stopped after six minutes or sooner if the subject vomited, requested termination of the test, or experienced a 3-fold increase in the magnitude of motion sickness on three consecutive occasions.

The geometric mean magnitude of gastrointestinal sensation increased most rapidly in the placebo group followed by the dimenhydrinate group; the ginger group exhibited a statistically significant slower increase compared to the other two groups. Whereas none of the subjects in either the placebo or dimenhydrinate groups were able to stay in the chair the entire six minutes, half of the ginger group was able to withstand the entire 6-minute duration (Mowrey & Clayson, 1982). This study was also limited by small test groups, as well as a lack of randomization and blinding.

The efficacy and safety of ginger in treating patients with hyperemesis gravidarum was tested in 27 pregnant women who were admitted to the hospital with hyperemesis and had not received relief of symptoms after two days (Fischer-Rasmussen, Kjaer, Dahl, & Asping, 1990). The study design was a double-blinded, placebo-controlled, crossover trial.

Patients were randomly selected to first receive treatment with either 250 mg of powdered ginger or 250 mg of lactose four times daily. After four days of treatment with the initial medication, a 2-day washout period was observed followed by another 4-day treatment phase with the alternative medication. Efficacy of treatment was evaluated on days 5 and 11 using a scoring system for symptom relief.

After randomization, both groups were found to be comparable in age, number of pregnancies, gestational age, and severity of symptoms. A statistically significant percentage (70.4%) preferred the period of ginger treatment compared to 14.8% who preferred the placebo period. The other 14.8% had no preference for either period. Symptom relief scores were significantly greater after treatment with ginger vs. placebo, particularly in reduction of nausea and vomiting. Of the 27 women who completed the study, one woman had a spontaneous abortion and one requested a legal abortion due to marital and social problems. The remaining 25 women delivered healthy infants without congenital deformities (Fischer-Rasmussen et al., 1990).

Daily dosages of 500 mg to 1000 mg of ginger were used in each of the five studies reviewed here. Side effects

were either not mentioned or found to be minimal. A side effect common in two of the studies was heartburn or gastric burning. Two of the studies that tested ginger's effects on postoperative nausea and vomiting revealed contradictory findings. Whereas one demonstrated lower postoperative nausea and vomiting compared to placebo and metoclopramide, the other demonstrated worsening nausea and vomiting with increasing doses of ginger. Two studies of ginger's efficacy in treating motion sickness also contradicted the other's findings. Both of these studies used very small test groups and failed to employ randomization and blinding. The study in pregnant woman with hyperemesis gravidarum involved a small treatment group but was otherwise well designed. This study's results exhibited statistically significant relief in nausea and vomiting and revealed no observable danger to the fetus.

Feverfew

Feverfew is most commonly placed in the genera *Tanacetum parthenium*; its name is derived from the Latin *febrifugia* which means fever reducer. Since 78 A.D., feverfew has been used to treat headaches, menstrual irregularities, stomachache, and fever. Its active

ingredient is believed to be the sesquiterpene lactone, parthenolide (Tyler, 1993). Of particular interest recently are this herb's purported beneficial effects in treating migraine headaches. One suspected pathogenesis of migraine is serotonin release by platelets during acute attacks. Feverfew extracts have been shown to inhibit serotonin release from platelets (Heptinstall, White, Williamson, & Mitchell, 1985). Though clinical trials in humans are few, the two known trials published in English showed favorable results.

Murphy, Heptinstall, and Mitchell (1988) conducted an investigation of the use of feverfew for migraine prophylaxis. The study design was a double-blinded, placebo-controlled, crossover trial. Sixty volunteers completed the 8-month study. Eligible participants were adults with a history of migraine headache problems of more than two years duration with at least one attack per month. All migraine-related medication was discontinued at the beginning of the study. Participants initially underwent a 1-month single-blinded placebo run-in period. Subjects were then randomized to receive either 1 feverfew capsule (mean of 82 mg or equivalent to 2.19 μ mol parthenolide) or matching placebo daily for four months. Thereafter, subjects received the opposite medication for an additional

four months. No washout period was utilized. Safety and efficacy were assessed every two months using patient diaries of migraine symptoms, adverse effects, visual or focal neurological disturbances, and working days missed due to migraine. A global assessment of patients' overall impressions of the treatment was also conducted.

Furthermore, a urinalysis, hematologic and biochemical tests, blood pressure, and pulse were checked during the 1-month run-in phase and after each 4-month treatment phase.

During feverfew treatment, subjects experience a 24% reduction in the number of migraine attacks. No significant reduction in the duration of attacks was reported, however. A non-significant trend toward milder headaches during feverfew treatment was noted, and a statistically significant reduction in migraine-associated nausea and vomiting was reported. Compared to 76 working days lost during placebo treatment, 68 working days were lost during feverfew treatment. Global impression assessments further demonstrated that feverfew was more effective than placebo. Mouth ulceration (10 instances) was the most frequently reported side effect during feverfew treatment, but no excess of other adverse events was noted. No significant changes in laboratory tests, blood pressure, or pulse were reported. The researchers

advised cautious interpretation of the low occurrence of side effects, considering the relatively short treatment period. Since treatment for migraine may be chronic, long-term studies on the safety of feverfew were advised (Murphy et al., 1988).

An earlier study recruited volunteers from a London migraine clinic (Johnson, Kadam, Hylands, & Hylands, 1985). Volunteers who met admission criteria were known to be self-treating with feverfew, had suffered classic migraines for at least two years, and had not experienced more than eight attacks per month. Subjects were informed that they would receive either feverfew or placebo. The trial design was a double-blinded, placebo-controlled, parallel group study. Patients were randomly assigned to receive either feverfew (25 mg) or an indistinguishable placebo, 2 capsules every morning with food for six months. Patients were instructed to treat acute attacks with aspirin or their usual medication. Presence and severity of visual symptoms, nausea, vomiting, and headache were recorded on diary cards, which were reviewed by investigators at 1 to 2 month intervals throughout the study. Although the frequency and number of tests is not specified, laboratory blood tests and urinalysis were also done.

Eight patients in the feverfew group and nine patients in the placebo group completed the study. Both groups were similar in the frequency of migraine before self-treatment with feverfew. In addition, both groups were comparable in the amount and duration of feverfew self-treatment and in the reduction of migraine frequency during prior feverfew use. In this study, the feverfew group reported fewer headaches than the placebo group. In the feverfew group, the frequency of headaches did not change compared to the frequency experienced during self-treatment. The placebo group, on the other hand, experienced a 3-fold increase in the frequency of migraine over that experienced while self-treating with feverfew. A statistically significant difference in the occurrence of nausea and vomiting was seen between the two groups, 39 episodes in the feverfew group compared to 116 in the placebo group. In addition, 42% of migraine attacks experienced by feverfew-treated subjects were associated with nausea compared to 79% of attacks in placebo-treated subjects. According to a global assessment of efficacy, a significantly greater number of subjects in the feverfew group thought they had benefited from treatment. Two subjects assigned to the placebo group experienced a recurrence of incapacitating migraine, thus dropped out of the study to resume feverfew self-treatment.

After following these two subjects for several months thereafter, the investigators reported that both had once again sustained a remission of migraine since resuming feverfew. Neither group experienced significant changes in blood pressure, heart rate, body weight, or hematologic and biochemical tests. Among the feverfew group, there was one report each of transient palpitations, abdominal pain, and heavier menstruation. Two cases of joint stiffness were also reported but were considered to be unrelated to the treatment. All patients in the placebo group reported at least one adverse event, which included nervousness, tension, tension headaches, insomnia, and fatigue. Despite the absence of significant side effects in the treatment group, authors acknowledged the paucity of scientific research and questioned feverfew's safety in long-term use (Johnson et al., 1985).

Feverfew studies reviewed here tested daily dosages of 50 and 82 mg. Results consistently demonstrated a reduction in the number of migraine headaches in subjects treated with feverfew vs. placebo. Both studies found statistically significant declines in episodes of nausea and vomiting associated with migraine. No significant side effects were exhibited in either study. A small test group weakens the validity of one study's results. Authors of

both studies recognized the potential need for long-term treatment of migraine. They cautioned against misinterpreting the meaning of few side effects found here in light of feverfew's unknown effects in long-term use.

Ginkgo Biloba

Native to China, the *Ginkgo biloba* tree was brought to Europe in 1730 and has subsequently become a popular ornamental tree throughout the world. The tree's fruits and seeds have been valued in China since 2800 B.C. In the last few decades, the concentrated extract of ginkgo biloba has become popular in Western medicine. Ginkgo biloba extract is believed to contain properties effective in treating conditions associated with decreased cerebral blood flow (e.g., short-term memory loss, headache, tinnitus, depression). Studies have shown that these effects are related to ginkgo's vasodilatory properties, and also due to the presence of flavonoids, terpenoids, and organic acids, which collectively act as free-radical scavengers (Le Bars et al., 1997; Tyler, 1993).

Le Bars et al. (1997) conducted a multicenter, double-blind, placebo controlled trial to assess the safety and efficacy of a ginkgo biloba extract in patients with Alzheimer disease (AD) and multi-infarct dementia (MID). A

total of 202 mildly to severely demented outpatients with a confirmed diagnosis of either AD or MID participated in the study. Initially, patients underwent a 2-week single-blinded placebo run-in phase. Thereafter, subjects were randomly assigned to treatment with either 40 mg of Ginkgo biloba extract (EGb 761) or matching placebo three times daily for 52 weeks. Adverse events, vital signs, pill counts, and drug dispensation were carried out at weeks 4, 12, 26, and 52. Primary outcome measures were assessed at weeks 0, 12, 26, and 52. Outcome measures included 1) cognitive impairment, measured with a cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog), 2) daily living and social behavior, measured with the Geriatric Evaluation by Relative Rating Instrument (GERRI), and 3) general psychopathology, measured with the Clinical Global Impression of Change (CGIC). A change or addition to patients' drug regimens of any substance with known cognitive function effects was not permitted throughout the study.

Following randomization, both treatment and placebo groups were found to have comparable characteristics at baseline. With regard to the ADAS-Cog, the EGb group showed no significant change at endpoint, whereas the placebo group exhibited significant worsening. The mean

treatment difference on this score significantly favored the EGb group. This relative improvement on the ADAS-Cog was interpreted as an equivalent to a 6-month delay in the progression of disease. The GERRI results exhibited a slight improvement in the EGb group and significant worsening in the placebo group, which ultimately revealed a statistically significant difference in favor of EGb. Both EGb and placebo groups exhibited a slight worsening on the CGIC. When attributing adverse events directly to the trial drug, 16% of the EGb group and 12% of the placebo group experienced at least one adverse effect. All of the most severe adverse events were transient and resulted in withdrawal from the study of only two participants in the EGb group and one in the placebo group. The authors concluded that EGb was safe and effective in stabilizing and improving the cognitive and social functioning of a substantial number of the demented patients tested over a six month to one year period (Le Bars et al., 1997).

Hofferberth (1994) carried out a double-blinded, placebo-controlled, parallel group study on the efficacy of EGb 761 in 40 hospitalized patients with a clinical diagnosis of Alzheimer Dementia. Patients were randomized to treatment with either 40 mg of EGb 761 or an identical placebo three times daily for three months. Primary and

secondary outcome measures, as well as compliance and adverse events were recorded at monthly intervals. The primary outcome measure was the SKT (cognitive tests for measuring memory and attention). Secondary outcome measures included 1) the Saccade Test which measured conjugated eye movements in response to a peripheral light stimulus, 2) measurement of reaction performance, 3) Sandoz Clinical Assessment Geriatric scale (SCAG) which measured psychopathologic changes, and 4) electroencephalography (EEG).

At the end of the 3-month treatment, a statistically significant improvement favoring the EGb group was shown by SKT scores. On the Saccade test, both saccade latency and saccade duration dropped significantly in the EGb group, representing a favorable outcome. In the placebo group, on the other hand, no effects on rapid eye movements were noted. The treatment group demonstrated improvements in all five subscales of the SCAG (i.e., cognitive disturbances, emotional disturbances, lack of drive, social behavior, and somatic disturbances). On reaction performance, subjects receiving EGb 761 were found to be superior in all tests. Likewise, this study recorded superior results in the theta/alpha quotient of the EEG and also in the global impressions of physicians (Hofferberth,

1994). Adverse effects, as well as changes in vital signs or laboratory values were not discussed. The results of this study should be cautiously interpreted, as the test groups were small and treatment duration was relatively short. Furthermore, the relevance of some outcome measures and their relation to clinical improvement is not clear.

Rai, Shovlin, and Wesnes (1991) conducted a double-blinded, placebo-controlled, parallel group study to investigate the effects of *Ginkgo biloba* in outpatients with mild to moderate memory impairment. Twenty-seven patients completed the study. Patients were randomly assigned to treatment with 40 mg of Ginkgo biloba extract (Tanakan®) or an identical placebo three times daily for six months. Outcome measures were assessed at weeks 0, 12, and 24. These parameters included the Folstein Mini-mental State Examination (MMSE), the Kendrick Battery for the detection of dementia in the elderly, a computerized version of the digit recall task, a computerized version of a classification task, latency and auditory event related potential (P300), and an EEG. Laboratory tests and urinalysis were done at baseline and at the end of the study. Adverse events were recorded and rated by the investigators throughout the study.

Despite a non-significant higher mean age of subjects in the placebo group, a baseline comparison between EGb and placebo groups of all outcome parameters confirmed the absence of significant differences. On the digit copying sub-test of the Kendrick Battery, the EGb group exhibited significantly superior scores at weeks 12 and 24. In addition, patients in the EGb group were found to be statistically superior on the median reaction time of the classification task at 24 weeks. Contradictory results were recorded by the EGb group on the digit recall test. Improvement in the form of decreased activity on EEG frequency of 1 to 3 Hz was noted in the EGb group, whereas the placebo group exhibited no statistically significant change. Neither group exhibited significant changes in the MMSE or the P300 (Rai et al, 1991). The occurrence of side effects or changes in laboratory tests was not mentioned. Like the Hofferberth study (1994), small test groups and the unclear relevance of some outcome measures limit the validity of some results.

Kleijnen and Knipschild (1992) scrutinized 40 clinical trials of *Ginkgo biloba* in cerebral insufficiency. According to their criteria, only 8 of the 40 were of acceptable quality. Shortcomings in these studies included small treatment groups and sketchy descriptions of

randomization procedures, participant characteristics, and outcome measurements. None of the trials employed double-blindedness. A brief review of six of the acceptable trials is included in this meta-analysis. Since none of these trials were published in English, it's worthwhile to note their findings here.

Schmidt, Rabinovici, and Lande (1991) treated 99 outpatients with cerebral insufficiency with either 150 mg of ginkgo extract or placebo daily for 12 weeks. Overall, patients' complaints improved 70% in the ginkgo group and 14% in the placebo group. Furthermore, physicians judged that 72% of the ginkgo group had improved compared to only 8% in the placebo group.

Bruchert, Heinrich, and Ruf-Kohler (1991) treated 303 outpatients with cerebral insufficiency with either 150 mg of ginkgo extract or placebo daily for 12 weeks. After 12 weeks of treatment the ginkgo group experienced significant improvement in 8 of 12 specified symptoms. Eighty-three percent of the ginkgo group and 53% of the placebo group recorded overall improvement. Physicians judged that 71% of those treated with ginkgo had improved compared to 32% of those from the placebo group.

Meyer (1986) treated patients who had complained of tinnitus, dizziness, and hearing impairment. Patients had

complained of these symptoms for an average of four to five months. The treatment consisted of either 160 mg of ginkgo extract or placebo daily for 3 months, and patients were followed for up to 13 months. In patients treated with ginkgo, improvement or absence of symptoms was seen after an average of 70 days, compared to 119 days for the placebo group.

Taillandier et al., (1986) treated 210 elderly patients who complained of dizziness, tinnitus, headaches, lack of energy, and concentration and memory impairments. The 12-month daily treatment consisted of either 160 mg of ginkgo extract or placebo. Outcome measures were assessed at 3, 6, 9, and 12 months. At 3, 6, 9, and 12 months the percentage of change from baseline experienced by the ginkgo group was 10%, 15%, 15%, and 17% respectively. The change in the placebo group was 4%, 4%, 8%, and 8% respectively.

Haguenauer, Cantenot, Koskas, and Pierart (1986) treated 70 patients with symptoms of tinnitus, headaches, nausea, and hearing loss of undetermined origin with either 160 mg of ginkgo extract or placebo daily for three months. Outcome parameters were assessed with a visual analogue scale and a 5-point ordinal scale. Among the ginkgo group, 47% no longer experienced symptoms at the end of treatment,

compared to 18% in the placebo group. According to the visual analogue scale, the ginkgo group experienced a 75% positive change from baseline compared to 18% in the placebo group.

Vorberg, Schenk, and Schmidt (1989) treated 100 patients with a mean age of 70 who had at least four of the following symptoms: concentration and memory difficulties, anxiety, dizziness, tinnitus, and headaches. Treatment consisted of either 112 mg of ginkgo extract or placebo daily for 12 weeks. After 12 weeks of treatment, the percentage improvement over baseline in the ginkgo group was 54% in concentration, 52% in memory, 48% in anxiety, 61% in dizziness, 65% in headaches, and 37% in tinnitus, vs. 19%, 17%, 23%, 24%, and 12% respectively in the placebo group.

In the above Ginkgo biloba studies, test dosages ranged from 112 mg to 160 mg daily. Ginkgo's effects on Alzheimer's dementia, multi-infarct dementia, and cerebral insufficiency were tested. The use of Ginkgo biloba vs. placebo exhibited favorable results in most outcome measures and each study showed significant improvement or protection against degeneration in at least one outcome parameter. One study found side effects in 16% of the treatment group, of which the most severe were transient.

All other studies did not mention whether any side effects had occurred. Outcome measures were poorly described and of questionable relevance in many of the trials. Although three of the above studies were of relatively sound design, a majority was neither double-blinded nor gave adequate descriptions of randomization or subject selection methods.

Saw Palmetto

The berries of *Serenoa repens*, commonly known as saw palmetto, come from the American dwarf palm tree that grows in sandy soil from South Carolina to Florida and west to Texas. Saw palmetto is used extensively in Europe to treat conditions associated with benign prostatic hyperplasia (BPH). The estrogenic sitosterols, as well as an unknown fat-soluble antiandrogenic component, are thought to account for its effects on the prostate (Tyler, 1993).

Although not a double-blinded, placebo-controlled trial, an investigation of saw palmetto's effects on voiding symptoms, urodynamic parameters, and prostate-specific antigen (PSA) is worth noting here. Forty-six men with previously untreated lower urinary tract symptoms (LUTS) were treated with 160 mg of saw palmetto twice daily for six months. An initial evaluation before the start of the study included an International Prostate Symptom Score

(IPSS), urinary flow rate, postvoid residual volume, digital rectal exam, serum PSA level, routine serum laboratory tests, and a urodynamic evaluation. Periodic assessments at 2, 4, and 6 months, included the IPSS, urine flow rate, and serum PSA levels, as well as the presence of any side effects. A postvoid residual volume and urodynamic evaluation was repeated after the 6-month treatment period. Also, objective evaluations of the degree of bladder outlet obstruction using the Abrams-Griffiths nomogram and Abrams-Griffiths number were done at baseline and again at the end of the study (Gerber, Zagaja, Bales, Chodak, & Contreras, 1998).

There was significant improvement from baseline in mean IPSS scores at 2, 4, and 6 months. The mean improvement in IPSS throughout the 6-month treatment was 34.1%, whereas 21 of the 46 subject experienced a 50% improvement at the end of six months of treatment. However, no significant changes were recorded in peak urinary flow rate, serum PSA level, or any of the urodynamic parameters. Subjects recorded no significant side effects from saw palmetto treatment and exhibited no change in serum laboratory tests. The authors recognized that the improvement in IPSS scores may have been the result of placebo effect, but claimed that the magnitude of

improvement was far greater than that seen in placebo groups in other randomized, placebo-controlled trials (Gerber et al., 1998).

The enzyme 5 α -reductase converts free testosterone to dihydrotestosterone (DHT), which promotes the synthesis of specific mRNA and proteins that further lead to a proliferative response in the prostate. Strauch et al. (1994) compared the 5 α -reductase inhibitory effects of a saw palmetto preparation (Permixon®) with a known inhibitor of 5 α -reductase, finasteride. The trial design was a comparative, placebo-controlled study. Thirty-two healthy male volunteers were randomly assigned to treatment with 5 mg of finasteride once daily, 80 mg of Permixon twice daily, or placebo once daily for 7 days. Serum testosterone and DHT levels were measured by radioimmunoassays at baseline and on each treatment day through 24 hours after the last dose of finasteride and 12 hours after the last dose of Permixon.

On day 8, DHT levels in the finasteride group experienced a statistically significant drop from 0.47 at baseline to 0.20 ng/ml. In contrast, the levels in the Permixon and placebo groups had dropped from 0.57 to 0.53 and from 0.54 to 0.51 ng/ml respectively; these changes

were not significant. In the finasteride group, Serum testosterone levels increased from 5.47 at baseline to 6.08 ng/ml at day 8. Subjects treated with Permixon experienced a concurrent change from 5.32 to 6.05 ng/ml and the placebo group's testosterone level dropped from 5.93 to 5.35 ng/ml. Subjects in both the finasteride and Permixon group experienced three clinical and one laboratory adverse effects each. None of these were considered serious and no subjects discontinued the study as a result. There was a mean increase in body weight of 1.0 ± 1.1 kg in the finasteride group and a mean decrease of 4.5 ± 5.7 mm Hg in sitting diastolic blood pressure in the Permixon group. All three groups experienced a statistically significant increase in serum albumin levels. The authors concluded that their findings confirm the inhibition of 5 α -reductase by finasteride and reject the claim that Permixon has the same effects (Strauch et al., 1994). Extremely small test groups, very short test duration, and the absence of blinding limit the value of these findings, however.

Champault, Patel, and Bonnard (1984) conducted a double-blinded, placebo-controlled trial on the effects of saw palmetto in 94 outpatients with BPH. Subjects were randomized to treatment with either 160 mg of Permixon or

placebo twice daily for 30 days. The following parameters were assessed before and after the 30-day trial: nocturia, intensity of dysuria, flow rate, post-micturition residue, and subjective rating by the patients and global rating by the physician.

Patients receiving Permixon exhibited significant improvement in all subjective and objective measures compared to those treated with placebo. The Permixon group reported five adverse effects and the placebo group reported 11. Of these reported side effects, all were considered minor. Furthermore, no significant changes in serum laboratory tests were noted in either group (Champault et al., 1984). A more detailed explanation of how outcome variables were measured and a more thorough presentation of the results were needed in this study.

Braeckman (1994) studied the safety and efficacy of saw palmetto in 305 patients with BPH. This study was a multicenter, open trial. All patients received 160 mg of saw palmetto extract twice daily for 3 months. Specific parameters were measured at days 0, 45, and 90. These parameters included mean and maximal urinary flow rates, mictional volume, residual urine volume (measured by transabdominal echography), prostate volume (measured by transrectal echography), urinalysis and culture, IPSS

score, and quality of life score measurements as recommended by the International Consensus Committee. On days 45 and 90, both patients and physicians gave a global evaluation of the treatment. On days 0 and 90, serum PSA values were measured.

At the end of the 90-day treatment, maximal and mean urinary flow rates showed statistically significant increases of 25% and 27% respectively. A non-significant increase in mictional volume was noted, whereas a significant decrease (20%) in residual volume was seen. Mean transrectal prostate volume significantly decreased by 10% at day 90. A significant improvement (35%) in mean IPSS scores was exhibited at the end of treatment. At day 90 the quality of life score remained unchanged in 19% of the patients, improved in 78%, and worsened in 3%. Eighty-eight percent of both patients and physicians viewed the treatment favorably at 90 days. Furthermore, PSA levels were not effected, which was viewed positively since a change may mask the development of prostate cancer during treatment. Of the 32 side effects recorded, none was considered serious and most were limited primarily to gastrointestinal complaints (Braeckman, 1994). The overwhelmingly positive results of this study should be

interpreted cautiously due to the study's lack of randomization, blinding, and control.

Of the three studies that showed positive outcomes, each tested daily dosages of 320 mg of saw palmetto. The fourth study tested 160 mg per day. Outcome parameters included various subjective and objective measurements. Two studies exhibited significant improvement in mean IPSS scores. Of these studies, however, one showed no significant change in peak urinary flow rates and the other demonstrated significant improvement in maximal and mean urinary flow rates. Two studies claimed significant reductions in post-void residual volumes. Side effects were few and none were significant. All of the studies had design shortcomings; two lacked blinding and control, another also lacked blinding and used small test groups and short test duration; another poorly explained how outcome parameters were measured and inadequately presented the results.

Summary of Literature Review

From the above review of clinical trials on selected herbal remedies, it is clear that some herbs have been more thoroughly and meticulously investigated than others. Based on the strength of study designs and consistency of

findings from these clinical trials, St. John's Wort, capsicum, and cranberry appear to have the strongest research support for efficacy. Valerian, peppermint, echinacea, feverfew, and ginkgo biloba have moderately strong support. And garlic, ginger, and saw palmetto have relatively weaker support for efficacy. Whereas the scientific evidence on a few of these herbs appears reliable and conclusive, evidence of reliability and efficacy on the majority is adequate at best. Some contradictory findings are present in a few studies. Methods and conclusions are difficult to interpret in others. The findings from a majority of the clinical trials reviewed here, however, exhibited relatively consistent findings, which indicate a measure of reliability. Furthermore, overall side effects were found to be minimal or insignificant.

CHAPTER 3 - METHODOLOGY

Project Design

The project design was tailored to meet specific objectives outlined in chapter one. These objectives were to provide information about herbal product regulation and manufacturing and to discuss inherent quality and safety issues. The objectives also included the provision of a detailed review of scientific literature on several selected herbs.

This limited introduction to herbal therapy was not meant to encourage or dissuade health care providers in the use of herbs in practice. Rather, the purpose was to provide an additional source of information about the use of herbal remedies. The intent was to inform and educate health care practitioners who have received little formal education in herbal medicine or who are simply interested in alternative medical therapies.

Cited advantages of offering education on alternative medical therapy were an impetus in the development of this project. Such advantages include the promotion of culturally sensitive care, practitioner focus on wellness and holistic care, and encouragement of patient self-care decisions and involvement (Hahn, 1997).

The Association of American Medical Colleges succinctly articulated another driving force behind this project. The Association emphasized that today's practitioners must be "sufficiently knowledgeable about both traditional and nontraditional modes of care to provide intelligent guidance to their patients" (Wetzel, Eisenberg, & Kaptchuk, 1998, p. 787).

Analysis of Data

This project was not a research study, and therefore contains no original data. The information regarding regulations, manufacturing standards, and quality and safety was obtained from refereed as well as popular literature. The data reviewed on selected herbs was found in previously performed clinical trials published in scholarly journals.

Regulations and Manufacturing Standards

Although herbal supplements are drugs, they are not regulated the same as pharmaceuticals. The basis for herb and other dietary supplement regulation in the U.S. is the Dietary Supplement Health and Education Act of 1994 (DSHEA).

In chapter two, the fundamental components of DSHEA were discussed. The information in this discussion was derived primarily from two sources. One source was the U.S. FDA's review/summary of the key points of DSHEA. This information was obtained from the FDA's official internet website at <http://www.fda.gov>. The second source was the U.S. Senate report 103-410 from the 103rd Congress, 2nd session. Information was taken from the report's summary of the bill.

Quality and Safety

A focus on providing practical guidelines for the reader was the motive for discussing quality and safety issues. Purchasing and utilization techniques were reviewed to guide the practitioner in employing herbs in practice and to provide a framework for responsible patient counseling. A brief review of potentially harmful herbs was included to help prevent the unscrupulous use or recommendation of such substances. Although not an exhaustive list, several herbs considered unsafe and unfit for human use were briefly reviewed. Guidelines for purchasing and utilization, as well as information on herbs considered unsafe, were based on recommendations from both popular and professional literature.

Clinical Trials

Clinical trials of eleven herbs were reviewed. Criteria for selecting the herbs included here were based on (1) the likelihood that a given herb would be encountered in a family practice setting and (2) the availability of clinical trials published in English on a given herb.

The likelihood of encountering any given herb in family practice is variable. The author's subjective experience and opinion partially influenced the choice of herbs included in this review. It is believed that the conditions for which the selected herbs are most commonly used are conditions that a general practitioners evaluate frequently. The selected herbs and conditions for which they are most commonly used to treat are as follows:

St. John's Wort - depression

Garlic - hyperlipidemia, hypertension

Valerian - insomnia

Peppermint - irritable bowel syndrome

Cranberry - urinary tract infections

Echinacea - upper respiratory infections

Capsicum - arthritis, post-herpetic neuralgia, diabetic
neuropathy

Ginger - nausea

Feverfew - migraine headache

Ginkgo biloba - memory impairment/dementia

Saw Palmetto - benign prostatic hypertrophy

In 1997, ten of the eleven herbs above were listed in the top 19 herb supplement sales in natural food stores in the U.S. (Blumenthal et al., 1998). This fact was also considered when choosing herbs that a health care provider would most likely encounter in family practice.

The availability of clinical trials published in English also influenced the selection of herbs included here. Although a majority of herbal research has been done in Germany, more and more research is being conducted and published in the U.S and Great Britain. The first step in locating clinical trials published in English was a literature search of the Medline database. Additional studies were then located from the reference lists of clinical trials obtained from Medline. A few clinical trials were discovered in a conference on herbal medicine sponsored by the colleges of health, nursing, and pharmacy at the University of Utah in May 1998.

Clinical trials that were randomized, double-blinded, placebo-controlled, and published within the last 10 years were sought. Approximately 60% of the clinical trials reviewed here met these criteria. This percentage is a

conservative estimate, however. Some trials contained all the above characteristics but were included in a meta-analysis of several trials, of which not all met the desired standards. Others lacked randomization or double-blindedness. A few met all the criteria but were older than 10 years.

In addition to the above criteria, several other characteristics were evaluated to determine the quality and validity of the research. These characteristics included sample size, test duration, consistency of findings, validity and reliability of instruments, relevance of outcome measures, and clarity of results.

CHAPTER 4 - PROJECT OUTCOME

Limitations

Like most other areas associated with health care, federal regulations governing the manufacturing and marketing of herbal products are continually revised, updated, or changed. The discussion of regulations included in chapter 2 is only a snapshot of current laws governing dietary supplements and their implications on quality and safety. A knowledge and understanding of current rules and regulations regarding herbal supplements is essential, but an informed health care provider should be continually observant of revised or newly created guidelines.

A discussion of herbs considered unsafe or unfit for human use was included to emphasize the potential hazards of using herbal products. The herbs listed in Appendix B are considered potentially harmful and should be used with caution, if used at all. This list of potentially harmful herbs, however, is a compilation of herbs discussed in current literature and is by no means an exhaustive list. Readers are advised to consult other publications for additional information on potentially harmful herbs (see Appendix C for additional resources).

Purchasing and utilization issues were discussed in chapter 2. Recommendations for purchasing the safest and highest quality products as well as for prudent utilization of herbal products were made. These recommendations were taken directly from those found in both popular and professional literature. Though the recommendations are thought to be good advice for any consumer of herbal products the author agrees with the aforementioned sentiment of Eisenberg (1997) that such advice remains incomplete and a matter of judgment as long as the efficacy and safety of these products cannot be assured.

As outlined in chapter 3, the selection criteria for the eleven herbs discussed here were partly subjective, which may limit the project's usefulness for other health care professionals. Clinical trials of the selected herbs were limited to research studies published or translated into English. This limitation excluded much of the herbal research that has been conducted in Germany and in other European countries.

Summary of Findings

A list of key points from the Dietary Supplement Health and Education Act of 1994 (DSHEA) and its implications on herbal product manufacturing, labeling, and marketing is

included here. More detailed information concerning this legislation and an extensive discussion of related quality and safety issues is found in chapter 2. Findings from reviewed clinical trials are also summarized.

Dietary Supplement Health
and Education Act of 1994

The following is a list of key findings from the review of DSHEA and its implications for dietary supplement manufacturing, labeling, and marketing. Although not governed directly by DSHEA, resultant advertising regulations established by the Federal Trade commission are also included below.

- Dietary supplements are defined as substances containing one or more of the following ingredients: vitamin, mineral, herb or other botanical, or an amino acid. A dietary supplement can also be a concentrate, metabolite, constituent, or extract of any of these ingredients.
- Dietary supplements must be intended for ingestion in tablet, capsule, powder, softgel, gelcap, or liquid form.
- Dietary supplements are not classified as pharmaceuticals as long as no medicinal or direct drug effect is claimed on the product label.

- Dietary supplement labels may describe how the product affects the so-called structure or function of the body or the well being achieved by its use. To make these claims, however, manufacturers must have substantiation that the claims are truthful and not misleading. Unless the FDA challenges a product's claims, manufacturers are not required to provide substantiation of these claims prior to marketing their product.
- The FDA carries the burden of proving a dietary supplement as unsafe. Until the FDA provides such proof, the FDA cannot remove a product from the marketplace.
- Dietary supplement advertisements may make claims regarding disease treatment and prevention, but manufacturers must provide substantiation for these claims. Substantiation is defined as competent and reliable scientific evidence, which is conducted and evaluated by qualified professionals.
- Advertisers must include the totality of research evidence, not just those that support their claims.
- Advertisements must include qualifying information such as side effects or whether an endorsee of the

product is being compensated or is qualified to make the endorsement.

- Advertisements may not claim that the FDA has approved the supplement.
- Under DSHEA, a dietary supplement is considered adulterated if it contains an ingredient that presents a significant or unreasonable risk of illness or injury when used as directed on the product's label.
- DSHEA granted the FDA authority to establish good manufacturing practices (GMPs), which govern the preparation and packing of dietary supplements. However, specific GMPs have yet to be introduced.
- A dietary supplement label must include a disclaimer that the FDA has not evaluated or approved the product's claims and that the product is not intended to diagnose, treat, cure, or prevent any disease.
- A label must identify the product as a dietary supplement, including the name and quantity of each ingredient.

- Unless covered by a specific U.S. compendium, the supplement must be the product identified on the label and contain the represented strength.
- Herbal product labels must identify the specific part of the plant from which the ingredients were derived.
- DSHEA established the Commission on Dietary Supplement Labels, which determines how best to provide truthful and scientifically valid information to the public.
- DSHEA mandated the creation of The Office of Dietary Supplements at the National Institute of Health, which promotes scientific research on the benefits of dietary supplements.

Findings from Reviewed Clinical Trials

A brief and general summary of findings from the clinical trials reviewed in this project follows. A more complete discussion of these findings is found in chapter 2. Appendix D contains additional usage information taken from other publications (see Appendix D).

- **St. John's Wort:** Findings of three studies and one meta-analysis support the efficacy of St. John's

Wort for the treatment of depression. The most common dosage tested was 900 mg/day of hypericum extract. The average test duration was 6 weeks. The most common adverse events were not specifically identified but were noted to be less than those experienced with tricyclic antidepressants.

- **Garlic:** Findings of one study and one meta-analysis support the efficacy of garlic for lowering serum cholesterol; two studies' findings refute this effect, however. Findings of another meta-analysis support garlic's efficacy in treating hypertension. The most common dosage tested was 900 mg/day of garlic powder, equivalent to 2.7 g/day of fresh garlic. The average test duration was 12 weeks. The most common adverse events were garlic odor and abdominal discomfort.
- **Valerian:** Findings of three studies support the efficacy of valerian in improving sleep quality. The most common test dosages ranged from 400 to 900 mg/day of valerian root extract. Test duration ranged from 2 to 9 nights. No adverse events were reported.
- **Peppermint:** Findings of four studies support peppermint's efficacy for treating the symptoms of

irritable bowel syndrome and non-ulcer dyspepsia, particularly abdominal pain. The most common dosages tested ranged from 270 to 561 mg/day of peppermint oil. The average test duration was 4 weeks. The most common adverse events were heartburn and perianal burning.

- **Cranberry:** Two studies' findings support the efficacy of cranberry in improving and reducing the severity and incidence of urinary tract infections. One study tested 300 ml/day of cranberry juice and the other tested 400 mg/day of cranberry solids. Both studies were 6 months in duration. Test subjects experienced no side effects.
- **Echinacea:** Two studies exhibited findings that support the efficacy of echinacea in reducing the severity and duration of flu-like and upper respiratory infection symptoms. Findings from three additional studies demonstrated enhanced immunomodulatory effects from echinacea use, whereas three other studies did not show this effect. The most common test dosages ranged from 900 to 1140 mg/day of echinacea purpurea root extract. The length of test duration ranged from 9 days to 8 weeks. No adverse events were reported.

- **Capsicum:** Findings of two studies support the efficacy of capsicum in improving the functional abilities for subjects with diabetic neuropathy (i.e. walking, working, and sleeping). Findings of another study support capsicum's efficacy in treating the pain of both osteoarthritis and rheumatoid arthritis. Another study's findings also support capsicum's efficacy in osteoarthritis but refute claims of efficacy in subjects with rheumatoid arthritis. A study of capsicum's efficacy in treating the pain of postherpetic neuralgia exhibited positive results. Findings of fourteen studies included in a meta-analysis support the efficacy of capsicum in treating the symptoms of diabetic neuropathy, osteoarthritis, rheumatoid arthritis, postherpetic neuralgia, psoriasis, and post-mastectomy pain. One study within this analysis contained findings that refute capsicum's efficacy in the treatment of pain associated with rheumatoid arthritis. The most common test dosage was 0.075% capsaicin cream applied topically four times daily. Duration of treatment ranged from 4 to 8 weeks. The most commonly reported adverse event was a burning sensation at the site of application.

All studies reported that this sensation diminished or disappeared with continued use of capsaicin.

- **Ginger:** Regarding ginger's efficacy in treating postoperative nausea and vomiting, the results of one study support this claim and results from another study refute it. In regards to ginger's efficacy in treating nausea and vomiting related to motion sickness, again one study's findings support this claim and another study's findings refute it. Results from an additional study support the efficacy of ginger in treating nausea and vomiting of hyperemesis gravidarum. The most common test dosages ranged from 500 to 1000 mg/day of powdered ginger root or fresh ginger. The most common adverse events were heartburn or gastric burning. In subjects with hyperemesis gravidarum, no dangers to the fetuses were observed.
- **Feverfew:** Findings of two studies support the efficacy of feverfew in the treatment of migraine headaches. Test dosages were 50 and 82 mg/day. Length of test duration was 6 and 8 months. The only significant adverse event was the development of mouth ulcers in some subjects.

- **Ginkgo biloba:** Two studies exhibited findings to support the efficacy of ginkgo in treating the symptoms of Alzheimer disease and multi-infarct dementia. Another study revealed contradictory findings regarding ginkgo's effects in memory impairment. Findings of six additional studies support the efficacy of ginkgo in treating the symptoms of cerebral insufficiency. The most common test dosages ranged from 112 to 160 mg/day of ginkgo biloba extract. Adverse events were either not specified or not reported.
- **Saw Palmetto:** Findings of three studies support the efficacy of saw palmetto in treating the symptoms of benign prostatic hypertrophy, whereas one study's results refute this claim. The average test dosage was 320 mg/day of saw palmetto. No significant adverse events were reported.

Implications and Recommendations for Further Study

As discussed above, with the exceptionally high costs of research and development for FDA approval and the inability to obtain patent protection on many traditional plant drugs, there is little incentive for the pharmaceutical industry or herb manufacturers to sponsor

studies on the safety and efficacy of most herbs. As Tyler (1993) has suggested, perhaps the best means to remedy this problem is to adopt the doctrine of "reasonable certainty" that is practiced in Germany. This practice emphasizes reasonable confidence in health care practitioners' clinical experience with plant drugs. This experience, in combination with evidence found in the literature and demonstrated by manufacturers, is then used to establish the overall safety and efficacy of herbal remedies.

Another, and likely more acceptable and legitimate means of establishing the safety and efficacy of plant drugs is to encourage the National Institute of Health (NIH) to sponsor more research on herbal medicines. Currently, the National Center for Complimentary and Alternative Medicine within the NIH is funding a clinical trial on St. John's Wort and also a pilot study of St. John's Wort in the treatment of juvenile depression. Through NIH supported research, perhaps more evidence in support of other popular herbal remedies will be established. With the establishment of such research-based evidence, trust in the use of herbal remedies among traditional health care practitioners is likely to grow. This trust may lead practitioners to more readily utilize herbal remedies to treat the numerous

conditions for which herbs have certainly shown a glimmer of promise.

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* Indicates studies included in a meta-analysis.

APPENDICES

APPENDIX A

PURCHASING AND UTILIZATION GUIDELINES

- Consider lifestyle or dietary changes before trying an herbal remedy (Herbal Roulette, 1995).
- Before considering an herbal remedy, one should be certain that the condition being treated does not require medical attention (Miller, 1996).
- Be skeptical of exaggerated assertions and do not believe unsubstantiated claims for miracle cures (Borins, 1998; Miller, 1996; Tyler, 1996).
- Seek information from objective sources rather than relying on promotional material or package information (Miller, 1996). Consult a well-researched guide on the use of herbs or obtain information on specific herbs from the American Botanical Council (Bilger, 1997).
- Encourage patients to consult their health care provider before using an herbal remedy and to discuss with the provider the use of any non-prescription products (Herbal Roulette, 1995; Miller, 1996; Rosenfeld, 1998).
- Be cautious about substituting an herbal product for a prescribed medication (Miller, 1996).

- Try to use only the best quality products—those with standardized materials (Tyler, 1996). Look for standardized extracts or for the word “standardized” on the product label (Bilger, 1997; Rosenfeld, 1998).
- Be cautious of any product that does not indicate or permit the calculation of the quantity of herbs contained in it (Tyler, 1996). Use products that clearly label all ingredients (Borins, 1998).
- The product label should contain the botanical name, the name and address of the manufacturer, a batch or lot number, the date of manufacturing, and an expiration date (Tyler, 1996).
- Carefully examine product labels to ensure that therapeutic levels of the desired herb are present (Tyler, 1996).
- Read labels skeptically and be aware of warnings. Note the herb’s positive and negative effects (Bilger, 1997; Herbal Roulette, 1995; Miller, 1996).
- Use single-ingredient products rather than those with a combination of ingredients (Bilger, 1997; Herbal Roulette, 1995; Miller, 1996).

- Try to use only brand name products made in the U.S. (Rosenfeld, 1998). Be cautious of products purchased or manufactured outside the U.S. (Borins, 1998).
- Start with low doses (Herbal Roulette, 1995). Do not take large quantities of any one herb (Huxtable, 1992).
- Herbs should not be recommended for use in pregnant women, lactating mothers, infants, or young children (Huxtable, 1992; Tyler, 1996).
- Elderly patients with impaired liver function, cardiovascular problems, or other serious conditions should be wary of using herbs, particularly long-term use (Tyler, 1996).
- Patients who take prescription medication that have known liver and kidney toxicities should be discouraged from taking herbs (Eisenberg, 1997).
- Observe for beneficial and harmful effects; stop taking an herb immediately if adverse effects occur; report any adverse effects to a health care practitioner, who should then report this to the FDA's MedWatch program (Anderson, 1996; Herbal Roulette, 1995; Miller, 1996; Tyler, 1996).

APPENDIX B

POTENTIALLY HARMFUL HERBS

- Comfrey (*Symphytum officinale*): contains hepatotoxic pyrrolizidine alkaloids. Several reports conclude that the ingestion of comfrey may cause hepatic veno-occlusive disease, which may lead to liver failure (Borins, 1998; Huxtable, 1992; Tyler, 1996). Animal studies indicate that lung, kidney, and GI problems are associated with comfrey ingestion (Herbal Roulette, 1995).
- Ephedra (*ma huang*): can elevate heart rate and blood pressure (Rosenfeld, 1998); may cause palpitations, nervousness, headache, insomnia, and dizziness (Tyler, 1993).
- Yohimbe (*Pausinystalia yohimba*): overdoses can lead to weakness and nervousness, followed by paralysis, fatigue, stomach problems, and ultimately death (Herbal Roulette, 1995). Yohimbe is a monoamine oxidase inhibitor, which necessitates the avoidance of tyramine. It should not be taken by persons suffering from hypotension, diabetes, or from heart, liver, or kidney disease. Psychic reactions

have also been noted after its ingestion (Tyler, 1993).

- Lobelia (*Lobelia inflata*): can both stimulate and depress the autonomic nervous system. Overdoses may result in respiratory depression, low blood pressure, diaphoresis, rapid heart rate, coma, and even death (Herbal Roulette, 1995; Tyler, 1993).
- Borage (*Borago officinalis*): safety and efficacy are questionable; contains hepatotoxic pyrrolizidine alkaloids (Tyler, 1996).
- Chaparral (*Larrea tridentata*): demonstrated as being extremely hepatotoxic (Gordon et al., 1995). Contains nordihydroguaiaretic acid which possesses considerable toxicity; feeding studies in rats produced lesions in the mesenteric lymph nodes and kidneys (Tyler, 1993).
- Coltsfoot (*Tussilago farfara*): contains both hepatotoxic and carcinogenic pyrrolizidine alkaloids (Huxtable, 1992; Tyler, 1996).
- Germander (*Teucrium chamaedrys*): Larrey et al. (1992) reported cases of seven patients who developed acute hepatitis following the use of Germander tea or capsules. Germander causes

hepatotoxicity due to the presence of diterpenoid derivatives (Tyler, 1996).

- Licorice (*Glycyrrhiza glabra*): can cause hypokalemia, hypertension, sodium and water retention, and cardiac problems (Borins, 1998). High doses for long periods of time produce pseudoaldosteronism (Tyler, 1996).
- Life Root (*Senecio aureus*): contains the hepatotoxic pyrrolizidine alkaloid senecionine (Tyler, 1993).
- Sassafras (*Sassafras albidum*): contains safrole, which is recognized as a carcinogenic agent in animals (Borins, 1998, Tyler, 1993).
- Pokerooroot (*Phytolacca americana*): has no therapeutic usefulness; contains the extremely toxic saponin mixture phytolaccatoxin; contains a proteinaceous mitogen, PWM, which may produce various blood cell abnormalities; may be fatal in children (Tyler, 1993).
- Scullcap (*Scutellaria lateriflora*): noted by several sources to be hepatotoxic (Anderson, 1996; Koff, 1995; MacGregor, Abernethy, Dahabra, Cobden, & Hayes, 1989).

- Blue Cohosh (*Caulophyllum thalictroides*): contains the glycoside caulosaponin, which is oxytocic, constricts coronary blood vessels, and causes intestinal spasms in small animals (Tyler, 1993).
- Broom (*Cytisus scoparius*): contains the alkaloid sparteine, which has negative chronotropic effects without positive inotropic effects; also stimulates uterine contractions; potential for *Aspergillus* infection if smoked (Tyler, 1993).
- Mistletoe (*Phoradendron leucarpum*): berries of both American and European mistletoe contain toxic proteins and are considered poisonous (Tyler, 1993); has also been suspected of causing hepatitis (Anderson, 1996; Borins, 1998).
- Dong Quai (*Angelica polymorpha*): contains furocoumarins that are prone to cause photosensitivity resulting in a type of dermatitis (Tyler, 1993). Noted to be a potential abortifacient (Borins, 1998).
- Jin Bu Huan: suspected of causing hepatitis (Anderson, 1996; Rosenfeld, 1998).
- Rue (*Ruta graveolens*): contains the furocoumarins, bergapten and xanthoxanthin, which can lead to

blistering of the skin following exposure to sunlight. The fresh plant may also cause gastric upsets if taken internally (Tyler, 1993).

- Canaigre (*Rumex hymenosepalus*): contains high levels of tannin, which may have considerable carcinogenic potential (Tyler, 1993).
- Devil's Claw Root (*Harpagophytum procumbens*): caution in use during pregnancy, may be a potential abortifacient (Borins, 1998).
- Barberry (*Mahonia aquifolium*, *M. nervosa*): caution in use during pregnancy, may be a potential abortifacient (Borins, 1998).
- Wormwood (*Artemisia absinthium*): contains absinthe, which can cause profound mental and physical changes. Its volatile oil contains thujone, which has caused convulsions and death in rats following injection, and has reportedly caused convulsions and unconsciousness in humans (Tyler, 1993).
Wormwood is also noted to have deleterious anticholinergic and hallucinogenic effects (Borins, 1998).
- Pennyroyal (*Hedeoma pulegioides*, *Mentha pulegium*): its volatile oil contains the extremely toxic

pulegone. Pulegone may cause severe liver damage in relatively small amounts (Tyler, 1993).

APPENDIX C

SUGGESTED RESOURCES FOR ADDITIONAL INFORMATION ON HERBS

Books

Tyler, V.E. *The honest herbal: A sensible guide to the use of herbs and related remedies* (3rd ed.). Binghamton, NY: Pharmaceutical Products Press; 1993.

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Foster, S. *Herbs for your health: A handy guide for knowing and using 50 common herbs*. Loveland, CO: Interweave Press, Inc.; 1996.

Periodicals

HerbalGram, published by the American Botanical Council, PO Box 201660, Austin, TX 78720.

*The Journal of Alternative and Complimentary Medicine:
Research on Paradigm, Practice, and Policy.* New York: Mary
Ann Liebert, Inc.

Internet Sites

American Botanical Council:

<http://herbalgram.org>

National Institute of Health National Center for
Complimentary and Alternative Medicine:

<http://altmed.od.nih.gov/nccam>

Herb Research Foundation:

<http://www.herbs.org>

Institute for Traditional Medicine:

<http://www.europa.com/~itm>

Health World Online:

<http://www.healthy.net>

Association of Natural Medicine Pharmacists:

<http://www.anmp.org>

U.S. Food and Drug Administration:

<http://www.fda.gov>

Federal Trade Commission:

<http://www.ftc.gov>

U.S. Department of Agriculture Agricultural Genome
Information System:

<http://probe.nalusda.gov>

APPENDIX D

ADDITIONAL USAGE INFORMATION FOR SELECTED HERBS

St. John's Wort

Popular Uses - Treatment of mild to moderate depression and anxiety.

Active Ingredient - Hypericin.

Mechanism of Action - May work through inhibition of dopamine, serotonin, norepinephrine, and gamma-aminobutyric acid (GABA) uptake; may have slight MAO inhibitory activity (Jellin, 1998).

Dosage - 2 to 4 g of dried herb or 0.2 to 1.0 mg of hypericin used in tea is thought to be effective when consumed daily for 4 to 6 weeks (Tyler, 1994); 300 mg three times daily of 0.3% standardized extract to deliver 1 mg of hypericin daily (Foster, 1996).

Adverse Effects - Photosensitivity is possible in light-skinned individuals (Blumenthal et al., 1998); serotonin syndrome has not been documented but thought to be possible considering the proposed mechanism of action (Jellin, 1998).

Drug Interactions - Potential to cause serotonin syndrome when combined with selective serotonin reuptake inhibitors, tricyclic antidepressants, monoamine oxidase

inhibitors, and bromocriptine; no interaction with tyramine-containing foods has been shown (Jellin, 1998).

Garlic

Popular Uses - Reduction of cholesterol and serum lipids, inhibition of platelet aggregation, and lowering of blood pressure.

Active Ingredient - Allicin.

Mechanism of Action - Mechanisms of lipid lowering effects are not clear, may affect thiol groups in many enzymes; there are conflicting results concerning garlic's ability to inhibit HMG-CoA reductase (Jellin, 1998). Anti-hypertensive and antiplatelet activity may originate in compounds affecting calcium-dependent processes; action of inhibiting platelet aggregation is speculated to result from the interference of thromboxane synthesis (Jellin, 1998).

Dosage - 4 g fresh garlic daily (Blumenthal et al., 1998); processed garlic preparations should deliver 5,000 mcg of allicin daily (900 mg/day of standardized garlic powder containing 0.6% allicin per 100 mg) (Foster, 1996). Dried garlic preparations should be taken in the form of enteric-coated capsules to ensure that the proper enzymatic

conversion of alliin to allicin can occur in the alkaline environment of the small intestine (Tyler, 1994).

Adverse Effects - Allergic reactions to garlic; heartburn and flatulence with larger doses (Tyler, 1994). Garlic odor may pervade the breath and skin (Blumenthal et al., 1998).

Drug Interactions - Although no cases of such interactions have been documented, garlic may interact with anticoagulant drugs such as warfarin (Jellin, 1998).

Valerian

Popular Uses - Minor tranquilizer and sleep aid.

Active Ingredient - Remains unidentified but may be a combination of volatile oil, valepotriates, and certain water-soluble constituents (Tyler, 1994).

Mechanism of Action - Thought to increase the levels of GABA in the synaptic cleft (Jellin, 1998).

Dosage - Two to three daily doses of tea prepared from 2 to 3 g of the dried rhizome and roots (Tyler, 1994); standardized 0.5% essential oil, 300 to 400 mg/day taken one hour before bedtime as a sleep aid (Foster, 1996).

Adverse Effects - Tyler (1994) considers valerian to be generally safe and free of side effects. Fatigue, abdominal cramping, mydriasis, and tremor were reported in

one case of valerian overdose; long-term use may lead to headaches, excitability, uneasiness, and cardiac disturbances (Jellin, 1998).

Drug Interactions - None known (Blumenthal et al., 1998).

Peppermint

Popular Uses - Spasmolytic of the gastrointestinal tract.

Active Ingredients - Volatile oil, primarily menthol (Tyler, 1994).

Mechanism of Action - Not specified.

Dosage - Average single dose 0.2 ml; average daily dose 0.6 ml in enteric-coated capsules (Blumenthal et al., 1998).

Adverse Effects - Capsules may occasionally open in the stomach causing heartburn; peppermint oil should not be used in persons with achlorhydria or in those with gallbladder or bile duct obstruction or inflammation (Foster, 1996). Avoid application to mucous membranes or use in infants and children, as this may produce a choking sensation (Foster, 1996; Tyler, 1994).

Drug Interactions - None known (Blumenthal et al., 1998).

Cranberry

Popular Uses - Prevention and treatment of urinary tract infections (UTI).

Active Ingredient - Fructose and a polymeric compound of unknown identity (Tyler, 1994).

Mechanism of Action - Inhibits colonization of E. coli bacteria by preventing their adhesion to epithelial cells that line the urinary tract and bladder (Foster, 1996; Tyler, 1994).

Dosage - For UTI prevention, 3 fluid ounces or 90 ml of cranberry juice cocktail daily (one-third of which should be pure juice); 12 to 32 fluid ounces or 360 to 960 ml daily of cranberry juice cocktail for the treatment of UTIs (Tyler, 1994). Capsules containing dried cranberry powder are also available, of which 6 capsules are said to equal 3 fluid ounces of juice cocktail (Tyler, 1994).

Adverse Effects - None found.

Drug Interactions - None found.

Echinacea

Popular Uses - Used as an immune stimulant, anti-viral, and anti-inflammatory agent; commonly used to treat colds and chronic respiratory tract infections (Jellin, 1998).

Active Ingredient - Includes cichoric acid, polysaccharides, flavanoids, and essential oils (Jellin, 1998).

Mechanism of Action - Stimulation of T-lymphocyte proliferation, interferon production, mobilization of other phagocytic leukocytes, and inhibition of hyaluronidase (Jellin, 1998; Tyler, 1994).

Dosage - 60 drops of *E. purpurea* root tincture or 1 g of dried root three times daily-not taken continuously, rather as needed at the onset of symptoms or in the early stages of infection (Foster, 1996). The German Commission E recommends that echinacea not be taken for longer than 8 consecutive weeks (Blumenthal et al., 1998).

Adverse Effects - Echinacea is contraindicated in progressive systemic diseases or infections such as tuberculosis, lupus, multiple sclerosis, AIDS, and HIV infection (Blumenthal et al., 1998; Jellin, 1998).

Drug Interactions - May interfere with immunosuppressive therapy (Jellin, 1998).

Capsicum

Popular uses - Treatment of pain associated with herpes zoster, diabetic neuropathy, arthritis, and post-mastectomy.

Active Ingredient - Capsaicin.

Mechanism of Action - Depletion of substance P, which mediates pain transmission from peripheral nerves to the spinal cord (Tyler, 1994).

Dosage - 0.075% capsaicin cream applied topically to painful areas 4 to 5 times daily for at least 4 weeks (Tyler, 1994).

Adverse Effects - Causes irritation to the mucous membranes and contact with the eyes must be avoided; can cause hypersensitivity reactions (urticaria) in rare cases (Blumenthal et al., 1998).

Drug Interactions - None known (Blumenthal et al., 1998).

Ginger

Popular Uses - Treatment of stomach upset and prevention of motion sickness.

Active Ingredient - Speculated to be galanolactone, a diterpenoid constituent of ginger (Jellin, 1998).

Mechanism of Action - Not clearly understood.

Dosage - 2 to 4 g of rhizome or equivalent preparation daily (Blumenthal et al., 1998). For motion sickness, powdered rhizome gelatin capsules 500 mg, two capsules 30 minutes before departure and one to two additional capsules as symptoms begin (Tyler, 1994).

Adverse Effects - Potential central nervous system depression and cardiac arrhythmias in large overdoses; inhibits thromboxane A₂, which compromises platelet aggregation and may cause bleeding (Jellin, 1998). The German Commission E cautions against ginger's use for morning sickness during pregnancy, however no evidence that ginger causes harm to the mother or fetus has been documented in the literature; German Commission E advises avoidance of ginger by persons with gallbladder disease (Blumenthal et al., 1998).

Drug Interaction - None known (Blumenthal et al., 1998).

Feverfew

Popular Uses - Prevention of migraine headaches.

Active Ingredient - Primarily parthenolide, a sesquiterpene lactone (Jellin, 1998; Tyler, 1994).

Mechanism of Action - Appears to reduce substrate for prostaglandin and leukotriene synthesis through inhibiting the release of arachidonic acid (Jellin, 1998). Probable inhibition of serotonin and histamine release from both platelets and leukocytes (Jellin, 1998; Tyler, 1994).

Dosage - 125 mg of dried leaves daily, provided the preparation has a minimum parthenolide content of 0.2%.

This is equivalent to chewing two average-sized fresh leaves per day (Foster, 1996). Most manufacturers produce tablets or capsules, each containing 300 mg of herb. At the 0.2% parthenolide concentration, one or less of these capsules daily will provide 125 mg of the herb or the adequate daily dose of 250 mcg of parthenolide (Tyler, 1994).

Adverse Effects - Can cause mouth ulcerations and swelling of the lips and gums in those who chew the fresh leaves (Foster, 1996; Jellin, 1998; Tyler, 1994). May produce bleeding through effects on platelet aggregation; reported to stimulate menstruation; is contraindicated in pregnancy and for use in pregnant mothers (Jellin, 1998).

Drug Interactions - Reduced effectiveness when used with NSAIDs or steroids; potential for bleeding when used with warfarin or other anticoagulants (Jellin, 1998).

Ginkgo Biloba

Popular Uses - Treatment for symptoms of cerebral circulatory disturbances (i.e., vertigo, tinnitus, memory loss, mood swings, and anxiety).

Active Ingredient - Flavanoids (ginkgoflavone glycosides) and terpenoids (ginkgolides and bilobalide).

Mechanism of Action - Flavanoids protect against capillary fragility and act as antioxidants (Jellin, 1998; Tyler, 1994). Ginkgolides inhibit platelet activating factor, which may improve circulation to the brain and increase brain tissue tolerance to hypoxia (Tyler, 1994).

Dosage - 120 to 240 mg of native dry extract daily, divided in two to three doses (Blumenthal et al., 1998). Ginkgo needs to be administered for 6 to 8 weeks before results are evident (Blumenthal et al., 1998; Foster, 1996; Tyler, 1994).

Adverse Effects - May include stomach or gastrointestinal upset, headache, and allergic skin reactions (Blumenthal et al., 1998; Foster, 1996; Tyler 1994).

Drug Interactions - Caution persons on anticoagulants (aspirin, warfarin, NSAIDs) to watch for bleeding (Jellin, 1998).

Saw Palmetto

Popular Uses - Used to treat symptoms associated with benign prostatic hyperplasia (urinary frequency, dysuria, nocturia) (Blumenthal et al., 1998; Jellin, 1998; Tyler, 1994).

Active Ingredient - Thought to be a combination of lipid extractable compounds such as sitosterols and various acids such as anthranilic, caffeic, and chlorogenic acid (Jellin, 1998; Tyler, 1994).

Mechanism of Action - Appears to be both anti-androgenic and anti-inflammatory (Jellin, 1998; Tyler, 1994). Liposterolic extracts of the berries reduce tissue uptake of both testosterone and dihydrotestosterone (DHT). Saw palmetto also inhibits 5-alpha-reductase, which reduces the conversion of testosterone to DHT. These actions decrease the proliferative effects of DHT on the prostate.

Dosage - 320 mg of standardized preparation daily or other preparations equivalent to 1 to 2 g of dried fruit daily (Blumenthal, et al., 1998; Foster, 1996).

Adverse Effects - Stomach upset in rare instances (Blumenthal et al., 1998; Foster, 1996).

Drug Interactions - May limit the effects of therapeutic androgens (Jellin, 1998).