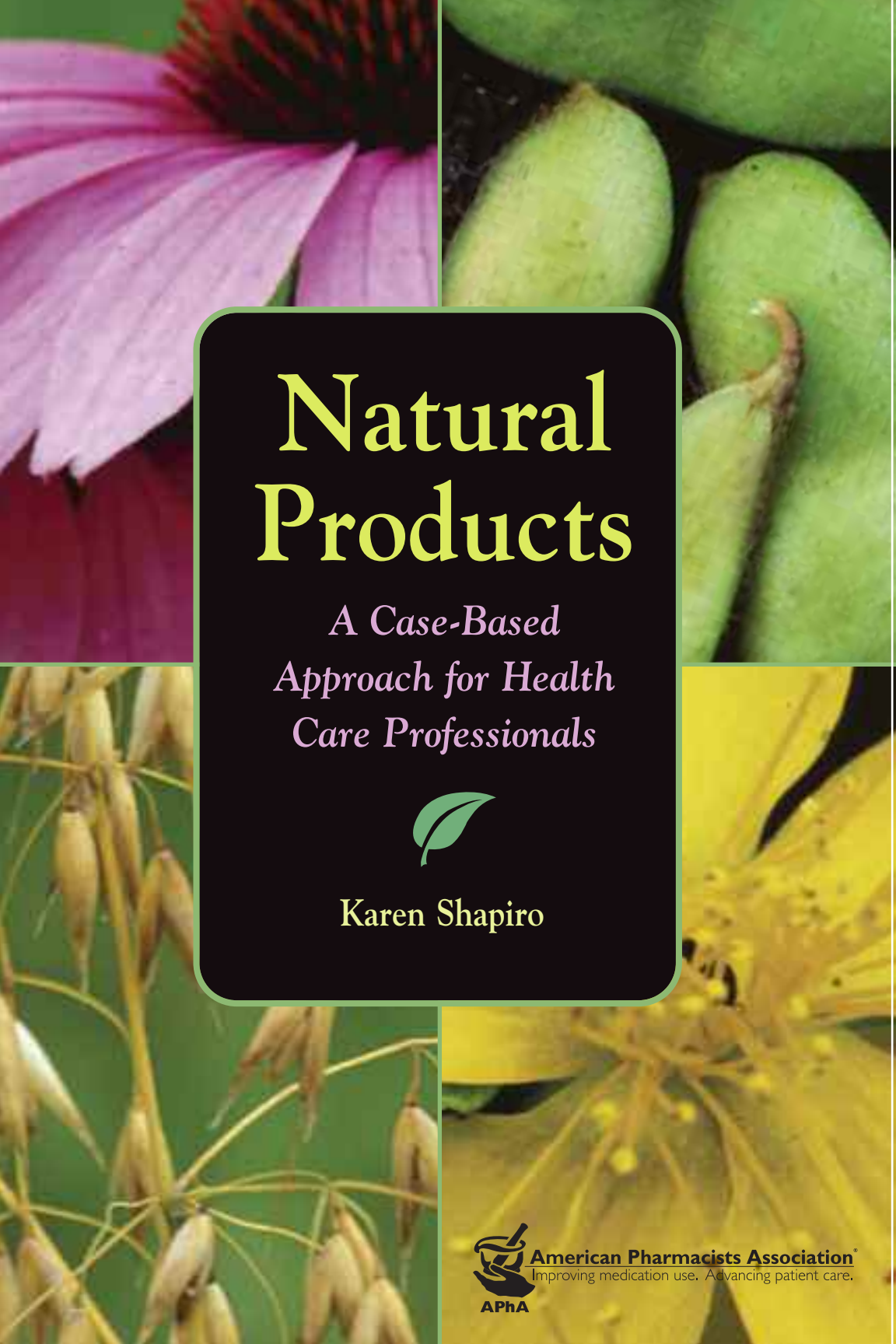

Natural Products

A Case-Based Approach for Health Care Professionals

Karen Shapiro

American Pharmacists Association®
Improving medication use. Advancing patient care.
APhA

Natural Products

A Case-Based Approach for Health Care Professionals

Karen Shapiro

Washington, D.C.

Contributing Authors

Jack J. Chen, PharmD, BCPS
Loma Linda University College of Pharmacy
Loma Linda, California

Eunice P. Chung, PharmD
Western University College of Pharmacy
Pomona, California

Christian R. Dolder, PharmD, BCPS
Wingate University School of Pharmacy
Wingate, North Carolina

Julia Ireland, DO
Private Practice
West Hollywood, California

Leila Khajehmolaei, PharmD
Los Angeles, California

James D. Scott, PharmD
Western University College of Pharmacy
Pomona, California

Karen Shapiro, PharmD, BCPS
Rancho Los Amigos National Rehabilitation Center
Los Angeles County Department of Health Services
Downey, California

Sandra Shibuyama, PharmD
St. Mary's Hospital
Long Beach, California

Winston Y. Wong, PharmD
Rancho Los Amigos National Rehabilitation Center
Los Angeles County Department of Health Services
Downey, California

Preface

I wrote this book to help schools and practitioners make a shift towards integrative medicine and to do my part to move medical practice from a disease-based to a healing-based approach.

Integrative medicine does not reject conventional medicine, nor does it accept unconventional practices without assessing them critically. It is a humanistic and fulfilling approach to medicine, and its benefits have been documented for both chronic and acute conditions. Natural products are one part of an integrative medicine approach.

Reading this book will give you a basic education in common natural products and the uses that are backed by solid evidence. Natural products can be helpful, harmful, or innocuous. I hope this text enables you to guide your patients so they use natural products in the most beneficial ways possible.

Karen Shapiro
Los Angeles, California
September 6, 2005

Dedication

This book is dedicated to my father, Jerry Shapiro. His sudden death this past year has caused an almost unbearable pain to me, to my sister Ruth, and to his many fellow travelers. We miss his appreciation of life.

To see a World in a Grain of Sand
And a Heaven in a Wild Flower
Hold Infinity in the palm of your hand
And Eternity in an hour.

—William Blake, "Auguries of Innocence"

Table of Contents

CHAPTER 1

Introduction to Natural Products

Karen Shapiro

The dietary supplement business is a $12 billion industry in the United States.[1] Nearly 19% of Americans used dietary supplements in 2002, up from 14.2% in 1998–1999. Among people over age 65, use more than doubled during the same period.[2] Compared with 1994, when about 4000 dietary supplement products were on the market in the United States, there are now about 29,000, with many more added each year.[3] Although single-ingredient products are predominant, the trend today is toward multiagent supple-

KEY POINTS

- Natural products are regulated according to the Dietary Supplement Health and Education Act (DSHEA).
- The DSHEA allows dietary supplements to be marketed with little or no proof of safety or efficacy.
- The FDA must prove that a dietary supplement is harmful in order to have it removed from the market.
- A "natural" product may have been chemically altered in a laboratory.
- "Natural" does not necessarily mean safer.
- Consumers must consider safety, efficacy, and quality when selecting a product.
- Natural products should be tested by a reputable agency for content, disintegration, and contamination.
- Resources exist to help in the selection of a reputable product.
- A clinician should choose an easily updated reference source for natural products since information in this area changes rapidly.
- Many natural products have dose–response relationships and may have lag periods for full response.
- Patients should use an appropriate dose and trial period and monitor response to individual agents.
- Natural products can be subject to polypharmacy; it is usually best to use individual, rather than combination, products.
- Some natural products increase bleeding risk.
- Some natural products are enzyme inducers and can lower the concentration of certain drugs.
- Patients should be encouraged to bring all prescription and nonprescription products to medical appointments.
- All adverse reactions involving dietary supplements should be reported using the FDA's MedWatch program.
- Care of the environment and safe farming practices should be considered.

ments—formulas for joint health or cholesterol control, for example—and sales of these combination products are growing faster than sales of individual agents.[4]

Reflecting the rising interest in natural products to treat illness and promote wellness, this text is designed as a practical learning tool to familiarize users with key facts and walk them through decision-making processes regarding popular natural supplements on the market today.

Products are discussed within the framework of common health conditions, such as depression or diabetes, and patient case scenarios are included to illustrate key points and to help master important considerations. A case-based learning approach, common in pharmacology courses, is one of the best ways to understand and retain knowledge. This book is not designed to be an exhaustive reference; many compendia, comprehensive reviews, and databases on natural products already exist for that purpose. Recommendations for reference sources are included in this chapter.

TABLE 1-1
Top 10 Natural Products Used by Adults in the United States (2002)

RANK	PRODUCT
1	Echinacea
2	Ginseng
3	Ginkgo
4	Garlic
5	Glucosamine
6	St. John's wort
7	Peppermint
8	Fish oil
9	Ginger
10	Soy

Source: *Reference 5.*

Understanding how to safely integrate standard and alternative care in practice is necessary not only to benefit patients (for example, fish oils have anti-inflammatory properties), but also for safety reasons (the product may be harmful). Countless cases have been reported of interactions between drugs and natural products, and other safety issues have come to light, such as hepatoxicity, effects on laboratory tests, and product contamination. With so many people using natural products, often without the advice of a health care provider, competent clinicians need to know each product's benefits and drawbacks, backed by research.

NATURAL PRODUCTS DEFINED

What actually is a "natural product?" The Dietary Supplement Health and Education Act (DSHEA), passed in 1994, defined natural products as "dietary supplements" and defined the term "dietary supplement" as a product containing one or more of the following ingredients:

- Vitamin
- Mineral
- Herb or other botanical
- Amino acid
- Dietary substance for use by humans to supplement the diet by increasing the total daily intake
- A concentrate, metabolite, constituent, extract, or combination of the listed ingredients.

The product must be intended for ingestion in pill, capsule, tablet, or liquid form and cannot be marketed for use as a conventional food or as the sole component of a meal or diet. According to the DSHEA definition, which is followed in this book, natural products include herbals or plant products, such as feverfew and ginkgo biloba, and nonplant products, such as glucosamine, coenzyme Q10, creatine, and others.

Natural products are not regulated like conventional drugs. DSHEA allows dietary supplements to be marketed with little or no proof of safety or effectiveness. Supplements marketed before DSHEA was passed were "grandfathered" in and considered safe for continued consumer use based on history and experience. Dietary supplements marketed after 1994 must provide "reasonable assurance" of safety based on their presence in the food supply, history of use, or other evidence that supports reasonable safety expectations.

The burden of proof is on the Food and Drug Administration (FDA) to determine which products might be unsafe. In other words, marketers of dietary supplements do not need to conduct large-scale studies to determine if their products are safe. If the FDA is concerned about the safety of a product, the agency must prove that the product poses a threat in order to remove it from the market.

Data on efficacy are not required for dietary supplements to reach the market, and as a result, they cannot make claims to treat, cure, or diagnose disease. Thus, it is illegal for dietary supplements to claim to "treat cancer" or "treat pain from arthritis." Instead, supplements can only make unscientific structure/function claims, such as "supports healthy circulation" or "strengthens immune function." Unfortunately these claims are so nonspecific and nonscientific that it is possible they do more harm than good, allowing supplement makers to imply that products have curative or health properties, in some cases without evidence.

EVIDENCE TO GUIDE DECISIONS

Efficacy of natural products is widely variable, ranging from no benefit to mild or significant benefit. This book uses an evidence-based approach to help ensure that decisions are based on sound information. Providing solid guidance is not a simple task, however, especially if study data are preliminary, poor, or insufficient. Sometimes the data for the use of natural products are observational. For example, women who consume a diet rich in soy products have been found to report significantly fewer hot flashes and other vasomotor symptoms of menopause, an observation that has led to keen interest in using soy products for symptom relief. Yet observational data can be proven wrong with clinical trials.

The choice in using any therapeutic agent, in the end, is up to the patient. The role of a clinician is to help guide rational decision-making. When patients want to use a natural product, they should be told about data insufficiencies and safety concerns.

Keep in mind that even when a product has been proven to be useless, the placebo effect can contribute to benefit—especially when the patient or someone they trust is helping guide the therapy.[6]

WHAT DOES "NATURAL" MEAN?

To consumers, the term "natural" often implies a safer product in comparison to conventional prescription medications, but "safer" is not always true. Natural products can be toxic and can be available in purified or manipulated forms as prescription drugs. Some chemotherapy drugs, including vincristine, vinblastine, and paclitaxel, as well as digoxin, colchicine, atropine, aspirin and some herbicides are plant-derived. Many plants produce chemicals whose purpose is to make sick or kill whatever bites into them. Major pharmaceutical companies have research teams devoted to finding new drugs from these often toxic (natural) plants in the rainforest. The bottom line is that safety depends on the particular product, not on whether it is termed "natural."

Everyone would likely agree that compounds found in the natural state and not structurally manipulated in a laboratory, such as plant extracts and desiccated plant products, are natural. What about a plant extract that has been manipulated in a laboratory to produce a different chemical compound? Pharmacologists refer to products that have been manipulated from raw materials as synthetic or semisynthetic.

Female hormone replacement therapy is a great example of the different ways in which terminology is used. Premarin®, the common form of prescription

estrogen, is made from desiccated mare (female horse) urine. The hormones present in the horse urine are not altered in any way. Premarin could be considered to be a "natural" product.

The hormones in Premarin do not match female human sex hormones—as expected, given that they come from a horse. Many women consider this product "unnatural" (to them) and prefer to use "bioidentical" hormone replacement therapy (BHRT). The estradiol used in BHRT is identical to the estradiol produced by a pre- (not post-) menopausal woman. BHRT estradiol is derived from plant precursors, which are manipulated in the laboratory to match female hormones. To the pharmacologist who tweaked the estradiol from plant product precursors in a laboratory, the end-product is synthetic. The hormone replacement product Cenestin® is advertised as a natural, plant-derived alternative to Premarin. At the bottom of the same advertisements, in small print, it reads "synthetic conjugated estrogens." Is Premarin, Cenestin, or BHRT safer? Which offers more symptom relief? Only well-designed clinical trials will answer these questions.

Cenestin is synthetic, despite being a plant-derived estrogen formulation

Glucosamine is a natural product used for osteoarthritis. The glucosamine present in joint supplement products is laboratory-derived from marine exoskeletons or is completely laboratory-manufactured. Glucosamine represents a natural product with good study data to support its use as a safer alternative to drugs such as ibuprofen, but its safety is not necessarily because it is "natural." In fact, there are "natural" nonsteroidal anti-inflammatory compounds similar to ibuprofen in food products in low doses, which could be concentrated and marketed—and would be expected to cause similar safety concerns as ibuprofen.[7]

Huperzine A, a compound derived from Chinese club moss, is advertised as a natural alternative to a class of drugs used to treat dementia, the acetylcholinesterase inhibitors. Yet the moss-derived compound has been manipulated structurally so that huperzine A is also an acetylcholinesterase inhibitor—not much different from prescription drugs in the same class, in either safety or effectiveness.

REPUTABLE RESOURCES

As in all therapeutics, competent clinicians know where to look when they need more information. Many textbooks are available that attempt to be inclusive and current, but in this rapidly changing field, they tend to be outdated by the time they come out in print. Rather than investing in natural product compendium texts, a better choice for clinicians who are grounded in the basics is to choose easily updated reference sources, such as those found online. Some key resources include the following:

- **The Natural Medicines Comprehensive Database** maintained by the Therapeutic Research Faculty is available in print, PDA, and online versions, and is the primary reputable source for natural product information. This resource provides clinically relevant information on more than 1000 products in an easy-to-use monograph format. References are linked for easy access to PubMed, and products are rated according to an evidence-based approach for safety and efficacy. Patient handouts and educational programs on hot topic areas are included. The online version is updated daily. The PDA version includes a checker for interactions between natural products and drugs. This resource is rated "superb" by a review in the *Journal of the American Medical Association*[8] and deemed "excellent" and "highly recommended" by the *Journal of the American Pharmacists Association*.[9] Web site: www.naturaldatabase.com.
- **The AltMedDex System,** part of the Micromedex Health Care Series Databases, is a reliable reference in a format many clinicians already use. Updated quarterly, AltMedDex covers dietary supplements and some form of alternative medicine. This service is available in many hospitals and clinics.
- **The Review of Natural Products,** published by Facts and Comparisons, is a well-referenced resource that includes more than 300 monographs describing clinical use, chemistry, pharmacology, interactions, toxicology, and important patient information. It includes most of the products patients are using. Web site: www.ovid.com.
- **The Natural Pharmacist Natural Medicine Encyclopedia,** by Steven Bratman and Richard Harkness, is a useful database of information on alternative medicine. It is not as thorough as the Natural Medicines Comprehensive Database but is easy to read and patient-friendly. An online version is free with a subscription to www.consumerlab.com (described below).
- **Office of Dietary Supplements, National Institutes of Health (NIH),** is a useful information source for patients and professionals. Fact sheets can be printed out on many common products and other helpful patient information is provided. Web site: http://ods.od.nih.gov.

- **The Cochrane Database of Systematic Reviews,** available online and on CD-ROM, provides succinct, well-researched summaries of many popular products. The database is published by the Cochrane Collaboration, a nonprofit resource for health care information known for rigorous quality standards. Web site: www.cochrane.org.

CHOOSING A REPUTABLE PRODUCT

This book covers the first step in deciding which products to recommend (or not recommend) to patients. The next step is knowing how to pick the right bottle on the shelf.

Product quality varies significantly. The bottle the patient selects may contain little active ingredient—or it may contain even more than is listed on the label. Contaminants can be present. The tablet might not disintegrate. Products can be manufactured under Good Manufacturing Practices (GMPs)—or not.

The following organizations offer helpful information on dietary supplements as well as seals of approval indicating that some of the tablets of a product were tested and found to pass the agency's requirements. Although seals from these agencies are an advancement, they do not imply in any way that the product will benefit the patient's condition. That information needs to come from one of the previously mentioned references.

- **The ConsumerLab** Web site is a valuable resource for selecting an appropriate product. Using samples chosen at random, this organization tests for product purity, content, disintegration (will the tablet break down in the gut and be absorbed?), and for harmful levels of contaminants. The ConsumerLab seal on a bottle indicates a passing mark. The Web site, which provides test results of most common products, is available to patients and practitioners at a minimal cost. Web site: www.consumerlab.com.
- **The U.S. Pharmacopeia (USP),** a nonprofit organization that sets Federal standards for prescription drugs and dietary supplements, has a natural product approval system called the Dietary Supplement Verification Program (DSVP).[10] USP also has a testing program similar to ConsumerLab that allows the USP seal of approval on supplements that meet the testing requirements. Web site: www.usp.org.
- **NSF International,** a company that sets standards for quality in food, water, air, and consumer goods, has a certification program based on product tests and adherence to Good Manufacturing Practices. The NSF seal of approval appears on more than 60 brands of dietary supplements. Web site: www.nsf.org.

CARING FOR USERS OF NATURAL PRODUCTS

Taking a blanket approach in clinical practice and disavowing the use of all natural products—which clinicians tend to do when they do not understand these products' use and fear drug interactions—can be harmful to patients. Why? Because patients, who will likely use natural products anyway, will avoid discussing them to avoid a reprimand.

It's helpful to ask patients to bring all medicines to the initial appointment, including "whatever you take for your health and medical conditions." Any new products can be brought to subsequent appointments. Be sure to specify that all formulations should be included, such as teas, powders, liquids, and pills. If a patient's native language is not English, a better response may be obtained if the information is requested in his or her own language.

The possibility of interactions is an important argument for being aware of all products a patient is using. The most typical problem is the use of additive agents that increase bleeding risk, which can be an issue for patients using anticoagulants (e.g., warfarin) or antiplatelets (e.g., aspirin and clopidogrel) and for those at an increased bleeding risk for other reasons. Another significant concern is natural products that can lower the concentration of drugs (e.g., St. John's wort), resulting in therapeutic failure.

Drug interactions are not the only issue. If a product has the potential to cause liver toxicity, for example, appropriate monitoring is warranted, and if a product is harmful in other ways, there is an obligation to discourage its use. Safety considerations may be more important than concerns regarding efficacy.

Instruct patients to quantify results from a product as best they can by using diaries, pain scales, or other monitoring tools. Counsel them to stick with a reasonable dose over a trial period. Just like conventional agents, natural products have dose–response relationships and may have lag periods before a full response is achieved.

Polypharmacy, the use of multiple medications by a patient, often for the same condition, extends to the use of natural products. When patients take many compounds, it is hard to determine which individual agent is causing harm or benefit. Combination products often contain agents used for any similar condition and can contribute greatly to polypharmacy. For example, combination weight loss products usually include agents used for diabetes high cholesterol along with other agents with no known benefit for any condition. Of course, some ingredients added to these products may not be harmful, such as small amounts of vitamin C and calcium.

A BRIEF HISTORY OF NATURAL PRODUCTS USE: PAST TO PRESENT

For most of human history, resources for treating disease were limited. Plant remedies were used long before written history. Plant products still in use today have been found in Neanderthal burial sites from 60,000 years ago.[11]

In the written record, the use of plants as medicine dates back 5000 years to the Sumerians, who recorded plant prescriptions on clay tablets. Around the same period the Chinese Emperor Chi'en Nung recorded the important uses of more than 3000 medicinal plants. In the first century AD, the contributions of Greeks and Romans were recorded by the Roman scholar Pliny the Elder and by Dioscorides, a Greek army surgeon, who wrote *De Materia Medica,* the first compendium of herbal remedies in the West. This volume contains identification and instructions on the medicinal use of nearly 600 plants.

Up until the time of Paracelsus (1493–1541), a Swiss physician whose work encouraged the search for "active constituents" of medicinal plants, plant medicines involved the use of whole plant products. In fact, the word "drug" is derived from the Dutch droog, which means a dried plant substance. Paracelsus' work helped lay the foundation for chemistry and manufacturing.

In the early 1800s, morphine was isolated from opium and quinine was isolated from cinchona.[12,13] and the first proprietary drugs appeared in the 1890s.[14] These discoveries helped found the field of phyto, or plant, chemistry. Today approximately 25% of modern drugs contain one or more active ingredients originally derived from plants, although the plant source may since have been replaced.[15]

Throughout the 1800s, the science of pharmacology developed as understanding of disease processes and organic chemistry advanced. In

A BRIEF HISTORY OF NATURAL PRODUCTS USE *continued*

1820, the first *U.S. Pharmacopoeia* was published. It outlined the properties, dosage, dosage forms, purity standards, and production standards for the "drugs" of the day—many of which were herbal products. In 1828, salicin, a precursor to aspirin, was extracted from willow bark. And in 1852, aspirin was first synthesized in a laboratory. In 1846, diethylether ("ether") was first used in surgery as an anesthetic. Many other drugs were identified during the early 1800s, including chloral (used today as chloral hydrate) and chloroform.

In the 1860's, high casualties from the Civil War and widespread outbreaks of communicable disease raised the demand for large quantities of medicines, contributing significantly to the rise of mass pharmaceutical manufacturing.

By the early 1900s, medical schools were cutting back on the study of botany in favor of pharmacology. Penicillin was discovered in 1928 when Sir Alexander Fleming observed that colonies of the bacterium *Staphylococcus aureus* could be destroyed by the *Penicillium* mold, proving that antibacterial agents could kill certain types of disease-causing bacteria.

By the late 1940s penicillin was being mass-produced and none of the U.S. medical schools was teaching herbal medicine. The pharmaceutical industry had taken off and new generations of synthesized drugs were being discovered. Medicine in the United States and the modernized world had switched from natural-product-based treatments to synthesized drug treatments.

In the 1960s there was renewed interest in getting back to nature. By the 1990s, use of what is now called "alternative" or "complementary" or "integrative" medical approaches was skyrocketing, driven in large part by a rise in chronic diseases such as asthma and diabetes and dissatisfaction with visits to the doctor's office.

In a brief patient visit, laboratory values may be addressed but the patient may feel forgotten. Today's medical care, divided into specialties and removed from a holistic approach, can appear to the patient as compartmentalized, depersonalized care. Although many clinicians do their best to combat this trend, patients are looking for treatments that give them a sense of power and self-direction over their course of therapy. The movement toward complementary medicine has led patients to seek out natural products and alternative healing techniques.

Combination products should usually, but not always, be discouraged. Occasionally, combination products can be useful, such as those combining multivitamins and policosanol, a cholesterol-lowering agent. When patients need both, the combination product reduces the number of daily pills they must take and simplifies the medication regimen. It may also be less expensive than buying both products individually.

Very few natural products have been studied for use in pregnancy and lactation or in children. Unless there is significant reason to recommend a product, and the safety profile is established, avoid recommending natural products to these groups. There are exceptions, such as the use of riboflavin and magnesium for migraine prophylaxis in pregnancy. Use a reputable reference source to check for safety if there is any doubt.

All adverse reactions involving natural products should be reported to the FDA's MedWatch Program at www.fda.gov/medwatch or by calling 800-FDA-1088.

Caring for the Environment

Unless a product can be manufactured ethically, its use should not be recommended. For example, cat's claw, a product used for many indications from asthma to HIV (with little evidence for efficacy) is harvested in the Peruvian rainforest. When natives harvest the vine, they replant and cultivate for the future, but opportunists ravage the vine and take no care for replacement. This product is not mass-produced and its use has caused damage to the rainforest.

In the 1960s, scientists discovered that an extract from the bark of the Pacific yew tree had anticancer properties. The active compound was identified as the chemotherapy drug paclitaxel. It took the bark of many of the slow-growing trees to treat one patient. Fortunately, a similar product was developed that can be derived semisynthetically from the needles of a relative of the Pacific yew.

The use of chemical fertilizers and pesticides, which introduce toxic compounds into the air, soil, and water—and ultimately the body—should be considered as well. Slow-growing plants, such as ginseng, can accumulate toxins over many years of growth.

One way to avoid the use of chemicals is to attempt to purchase organically grown plant products. These are not always available, but fortunately the number of reputable products that are organically grown is increasing.

SELF-ASSESSMENT

1. Which is TRUE concerning natural products:
   a. Medicinal plant products were found in human burial sites dated to 60,000 years ago.
   b. Dioscorides recorded the medicinal use of plants in his *De Materia Medica*.
   c. Many drugs today are plant-derived.
   d. All of the above.

2. The Dietary Supplement Health and Education Act was passed in:
   a. 1910
   b. 1920
   c. 1994
   d. 2004

3. Dietary supplements, similar to drugs, must be proven safe prior to marketing.
   a. True
   b. False

4. A mushroom mixture claims to "treat cancer" on the bottle label. This labeling is:
   a. Legal
   b. Illegal

5. A mixture of lipid-lowering products claims to "support healthy cholesterol levels" on the bottle. This labeling is:
   a. Legal
   b. Illegal

6. A manufacturer can market a product without studies demonstrating safety. Who is responsible for removing the product from the market if it proves to be unsafe?
   a. The manufacturer
   b. The NIH NCCAM
   c. The FDA
   d. None of the above

7. Natural products are often plant-derived. Care should be taken to protect the environment and to limit the use of harmful chemicals.
   a. True
   b. False

8. **Bioidentical hormone replacement therapy (BHRT) is promoted as a natural way to treat menopausal symptoms. A patient using this therapy tells you that it is much more natural and safer than hormones made from a horse. Which of the following is correct?**
   a. BHRT products contain only dessicated plant extracts.
   b. The hormones in BHRT are derived from plant precursors.
   c. The hormones in BHRT match those found in human females.
   d. b and c only

9. **A patient with knee osteoarthritis wishes to try glucosamine. She is told by her clinician to go to the pharmacy and purchase the cheapest brand. This advice is:**
   a. Reasonable; all products are likely to be similar in quality
   b. Not reasonable; a reputable product should be chosen

10. **Seals of approval for product quality are issued by the following agencies:**
    a. ConsumerLab
    b. USP
    c. NSF
    d. All of the above

Answers: 1-d; 2-c; 3-b; 4-b; 5-a; 6-c; 7-a; 8-d; 9-b; 10-d

REFERENCES

1. *Alternative Medicine*. Harvard Medical School, Palm Coast, FL: Harvard Health Publications; 2003.
2. Kelly JP, Kaufman DW, Kelly K, et al. Recent trends in use of herbal and other natural products. *Arch Intern Med*. 2005;165(3):281–6.
3. Atwater J, Montgomery-Salguero J, Roll DB. The USP Dietary Supplement Verification Program: helping pharmacists and consumers select dietary supplements. *US Pharm*. 2005;6:61–4.
4. Available at http://nccam.nih.gov. Accessed August 20, 2005.
5. Barnes P, Powell-Griner E, McFann K, et al. Advance Data Report 343. Complementary and alternative medicine use among adults: United States, 2002. May 27, 2004.
6. Gibbs WW. All in the mind. Fact or artifact? The placebo effect may be a little of both. *Sci Am*. 2001;285(4):16.
7. Beauchamp GK, Keast RS, Morel D, et al. Phytochemistry: ibuprofen-like activity in extra-virgin olive oil. *Nature*. 2005 Sep 1;437(7055):45–6.

8. Marty AT. Review, Natural Medicines Comprehensive Database. *JAMA*. 2000;283:2992–3.

9. Assessment of the quality of reference books on botanical dietary supplements. *J Am Pharm Assoc*. 2002;42(5):723–34.

10. Available at www.usp.org/USPVerified. Accessed August 20, 2005.

11. Rudgely R. *The Lost Civilizations of the Stone Age*. New York: The Free Press; 1999.

12. Cule J. *The Timetables of Medicine*. New York: Black Dog and Leventhal Publishers; 1999.

13. Jurna I. Sertürner and morphine—a historical vignette. *Schmerz*. 2003;17(4):280–3.

14. Haas LF. Pierre Joseph Pelletier (1788–1842) and Jean Bienaime Caventou (1795–1887). *J Neurol Neurosurg Psychiatry*. 1994;57(11):1333.

15. Nature's Pharmacy: Ancient Knowledge, Modern Medicine. Available at www.uihealthcare.com/depts/medmuseum/galleryexhibits/naturespharmacy/naturepharmacy.html. Accessed January 11, 2005.

CHAPTER 2

Dementia

Karen Shapiro and Jack J. Chen

Alzheimer's disease is the most common form of dementia, affecting about 4.5 million men and women in the United States. The incidence of Alzheimer's disease increases with age, and it affects up to 50% of people older than 85 years of age. Since Alzheimer's is the most common form of dementia, natural products used for dementia are usually studied in Alzheimer's patients. However, ginkgo biloba, the most popular product used for dementia, has been studied in other types of dementia and in other types of cognitive dysfunction.

Gingko biloba

Alzheimer's disease requires a careful diagnosis prior to any treatment recommendation. Occasionally, dementia may have an identifiable cause and be treatable. Causes could include, among other things, a vitamin deficiency or severe depression. In most cases, the dementia cannot be cured and the best prescription agents offer only temporary improvement or a modest delay in symptom progression.

Most patients with moderate-to-severe Alzheimer's disease will likely be offered a

KEY POINTS

- Ginkgo biloba may provide modest benefit in dementia.
- Ginkgo biloba products should be standardized and tested for content.
- Ginkgo biloba extract inhibits platelet-activating factor and can increase bleeding risk.
- Ginkgo biloba supplements should be discontinued prior to elective surgery.
- Huperzine A has the same mechanism of action as the prescription acetylcholinesterase inhibitors.
- Vitamin E supplementation may be useful for slowing disease progression; however, the high doses used for dementia can contribute to an increase in all-cause mortality.

prescription drug. A few alternative agents in common use include ginkgo biloba, huperzine A, and vitamin E.

GINKGO BILOBA

Ginkgo biloba is the best-selling plant medicine in Europe, where it is used for Alzheimer's disease, vascular dementia, peripheral claudication, and tinnitus. It is one of the top selling natural products in the United States. Ginkgo biloba extract is made from the leaves of the ginkgo tree, one of the oldest tree species on Earth. The leaves have two lobes, and thus the name biloba. Most of the ginkgo leaf used commercially comes from the Sumter plantation in South Carolina, where more than 12 million Ginkgo trees are cultivated.

PRODUCT	DOSAGE	EFFECT	SAFETY CONCERNS
Ginkgo biloba	120 to 240 mg daily, divided twice daily, in a product labeled to contain 24% flavone glycosides	Majority of studies support benefit for modest memory improvement	• Primary side effects are gastrointestinal complaints • Possibility of allergic skin reactions, including serious rash • Do not consume large amounts of ginkgo seed due to seizure risk; ginkgo supplements may decrease seizure threshold • Inhibits platelet-activating factor causing increased bleeding risk • Can decrease concentration of omeprazole and possibly other drugs
Huperzine A	100 to 200 mcg/day	May be as effective as the prescription acetyl-cholinesterase inhibitors—modest delay in symptom progression	• Gastrointestinal side effects • No additive benefit with prescription agents in same class—yet increased risk of toxicity
Vitamin E	1000 to 2000 IU/day	May slow rate of disease progression	• Do not recommend; dosage used for dementia unsafe

Ginkgo leaf extract contains many different flavonoids and terpenoids that have been studied individually and in combination. While some of the individual components may provide benefit, more benefit is derived from using the whole-leaf extract. Most products used in clinical studies have contained 24% to 25% flavone glycosides and 5% to 6% terpenoids (bilobalide and ginkgolides). Many products available to consumers do not contain these concentrations.[1]

The exact mechanism of action of ginkgo biloba extract is not well understood. The extract possesses anti-inflammatory properties and may help protect neurons from damage. Oxidative injury may develop secondary to

PATIENT CASE

MR. WALLACE

Mr. Wallace is a 72-year-old retired college professor who was diagnosed with Alzheimer's disease at a clinic visit. His wife had brought him to the doctor with concerns about her husband's memory. She stated that he frequently walked into rooms and forgot why he had gone there. She reported that his ability to recall things that had happened to him was diminished.

For example, his son and daughter-in-law had visited from the East coast, and a few days afterward he asked his wife when they were coming to visit. On one occasion he went to the store to pick up a few grocery items and returned 3 hours later, unable to account for why he was gone so long. He was prescribed donepezil 10 mg nightly. His other medications include warfarin for atrial fibrillation and benazepril for hypertension.

At his second clinic visit 10 months later, he is demonstrating significant decline in his cognitive function. At the initial appointment, when given four words, he was able to remember one after 5 minutes. Today, he cannot recall any of four given words and he does not recall being asked to memorize any words. At the previous visit, he was able to name a watch and pen, but he had some difficulty naming unusual objects—he called the watch buckle "a thing for closing it" and was unable to generate the name for a shoelace. Today, he could not name his watch and some other simple items.

His wife reports that he often forgets her name, which she finds particularly upsetting. She is concerned that his mood has worsened and he is sometimes irritable and angry. She states she is getting scared and is not sure if she will be able to care for him if his condition continues to worsen. She asks if ginkgo biloba, huperzine A, or vitamin E would help. She has been investigating Alzheimer's dementia on the Internet and is aware that people are using these products.

beta-amyloid-induced free radicals, inadequate energy supply, and inflammation. It is thought that when normal brain molecules are disrupted as a result of inflammation, amyloid beta proteins in the brain can misfold. Misfolded amyloid beta proteins are thought to have a critical role in the development of Alzheimer's dementia. The flavonoids have potent antioxidant and free radical scavenging properties.[2] Ginkgolides are selective antagonists of platelet aggregation induced by platelet-activating factor, an inflammatory mediator. [3–6]

The majority of evidence supports the use of ginkgo biloba as beneficial for modest memory improvement in patients with dementia.[7–9] One widely reported study in 1997 found no benefit; however, this study has been widely criticized for problems with study design.[10] Ginkgo biloba extract may not be as beneficial as acetylcholinesterase inhibitors, the typical first-line agents.[11] Many patients take both products together. A typical dose of ginkgo biloba for dementia is 120 to 240 mg/day, divided twice daily, in a tested product found to contain 24% flavone glycosides.

Safety Considerations/Drug Interactions

In the majority of patients, ginkgo biloba is well tolerated. The primary side effects are gastrointestinal complaints. A small number of patients report headache, dizziness, and allergic skin reactions.[12] Skin reactions, including serious rash, have occurred with the use of ginkgo taken orally. Gingko should not be used topically because it can irritate the skin. Ginkgo seeds contain a neurotoxin that can cause seizures if consumed in large amounts.[13] Ginkgo can lower the concentration of omeprazole, and possibly other proton pump inhibitors and other drugs.[14]

Due to platelet-activating factor inhibition, there have been numerous reports of ginkgo-associated bleeding.[15,16] Clinicians should consider whether concurrent use with warfarin, aspirin, or other antiplatelet agents and other natural products that increase bleeding is worth the risk. One study found no increase in the international normalized ratio (INR) in patients using both ginkgo and warfarin.[17] This means that the clinician may not be aware that the patient is at an increased bleeding risk. Ginkgo should be discontinued for at least 3 days and preferably longer (some clinicians recommend up to 2 weeks) prior to surgery.[18] Ginkgo has a short half-life, but the effect on platelet-activating factor is longer.

Huperzine A

Huperzine A is an acetylcholinesterase inhibitor derived from a particular type of Chinese club moss (*Huperzia serrata*) and then chemically purified.

Acetylcholinesterase inhibitors are an established therapy for Alzheimer's disease and dementia. The acetylcholinesterase inhibitors work by blocking the degradation of acetylcholine, a neurotransmitter that is important in learning and memory. Acetylcholine is greatly diminished in the brains of patients with Alzheimer's disease.

Huperzine A

It is interesting that huperzine A is marketed as a natural product. It is made from a plant, but the plant extract then requires lab manipulation. By this definition, some of the chemotherapeutic drugs and many others (digoxin, colchicine, etc.) that are plant-derived would be considered "natural." This emphasizes the fact that natural may or may not mean safer. In this case, the product is relatively safe, but whether it is "natural" depends on the user's definition.

The available data suggest that huperzine A may be as effective as the prescription acetylcholinesterase inhibitors.[19,20] It may also be neuroprotective.[21] The duration of action and enzyme specificity is longer than tacrine, an older acetylcholinesterase inhibitor.[22] Typical doses used for dementia are 100 to 200 mcg/day.

Safety Considerations/Drug Interactions

Huperzine A, similar to other acetylcholinesterase inhibitors, can cause gastrointestinal upset. Much higher doses than those recommended here could theoretically cause cholinergic toxicity. Symptoms of cholinergic toxicity include bradycardia, bronchial hypersecretion and bronchoconstriction, skeletal muscle fasciculation and twitching, ataxia, and seizures. Huperzine A should not be taken concurrently with the prescription acetylcholinesterase inhibitors.

Vitamin E

Vitamin E (α-tocopherol) is an antioxidant that prevents cellular damage. Free radicals contain an unpaired electron that can cause oxidative damage to cells and result in cell death. Antioxidants, such as vitamin E, prevent this damage by binding to the free radical and neutralizing the unpaired electron. Vitamin E is present in many oils, grains, nuts, and fruit. The Recommended Daily Intake (RDI) for vitamin E is 15 mg (equivalent to 22 vitamin E IUs of natural α-tocopherol or 33 vitamin E IUs of synthetic vitamin E) and is easily obtained from the diet.

A randomized, blinded trial with 341 subjects compared vitamin E 2000 IU/day to selegiline or placebo. Subjects taking vitamin E had a slower rate of disease progression (by 200 days) than placebo, and similar to the delay seen with subjects taking selegiline. Death was not delayed in either group.[23] A retrospective chart review of 130 patients found that vitamin E supplementation of at least 1000 IU/day might slow disease progression.[24] The data are not conclusive, but appeared promising until more recent results concerning vitamin E safety became available (see Safety Considerations/Drug Interactions). The studies for dementia used doses of 1000 to 2000 IU/day.

Safety Considerations/Drug Interactions

Doses of vitamin E for dementia are much higher than the RDI. Previously, high doses of vitamin E were thought to be innocuous, but this is no longer true. A meta-analysis involving 135,967 participants in 19 clinical trials studying the use of vitamin E found a statistically significant relationship between vitamin E dosage and all-cause mortality, with increased risk of dosages greater than 150 IU/day. The study concluded that doses greater than 400 IU/day should be avoided.[25,26]

Patient complaints from vitamin E supplementation are uncommon, except for the occasional gastrointestinal upset. High doses of vitamin E can elevate the INR and should be used with caution, if at all, in patients taking warfarin or antiplatelet agents.

Patient Discussion

Mr. Wallace is demonstrating more advanced disease and may be a candidate for a drug such as memantine, an N-methyl-d-asparate- (NMDA-) receptor antagonist. Alzheimer's disease is progressive and his condition will eventually worsen. The addition of a natural product might provide some mild benefit, but not to the extent that his wife requires. At this point, the caregiver (the wife) requires assistance with her husband's care.

Ginkgo biloba is the best-studied product and can be recommended for use in most patients. This patient is taking warfarin and the clinician must consider the increased risk of bleeding prior to recommending use. Although the INR may not be elevated secondary to ginkgo use, the risk for bleeding, due to platelet-activating factor inhibition, will be elevated.

Huperzine A should not be recommended for this patient, who is already using a drug, donepezil, with the same mechanism of action. Vitamin E, at high doses, may be detrimental and should not be recommended at this time.

SELF-ASSESSMENT

1. Which is TRUE concerning ginkgo biloba:
a. The tree is one of the oldest living tree species on Earth.
b. Components of the plant extract are thought to work together to provide benefit.
c. Ginkgo biloba extract has anti-inflammatory properties.
d. All of the above.

2. Which of the following agents inhibits platelet-activating factor?
a. Ginkgo biloba
b. Huperzine A
c. Vitamin E
d. None of the above

3. Which is the correct dose of ginkgo to recommend for dementia?
a. 1 to 2 mg/day
b. 120 to 240 mg/day
c. 0.2 mcg/day
d. None of the above

4. Which is TRUE concerning ginkgo biloba:
a. The seeds contain a neurotoxin which can cause seizures.
b. Chewing the seeds is the best way to treat dementia.
c. Ginkgo can be recommended as a topical agent.
d. Ginkgo poses no risk for serious skin rashes.

5. Which is TRUE concerning huperzine A:
a. It can be recommended for use in patients taking donepezil.
b. The mechanism of action involves blocking the dopamine receptor.
c. Gastrointestinal upset is possible.
d. Cholinergic toxicity is likely with recommended doses.

6. Which is TRUE concerning vitamin E:
a. Rich food sources include many oils, grains, nuts, and fruit.
b. Most people get adequate vitamin E through the diet.
c. Vitamin E is a potent antioxidant.
d. All of the above.

7. Which is TRUE concerning vitamin E:
a. The RDI is 15 mg.
b. 15 mg is equivalent to 22 IU of natural a-tocopherols.
c. 15 mg is equivalent to 2000 IU of natural a-tocopherols.
d. A and B

8. Which is TRUE concerning vitamin E:
   a. Doses of 2000 IU/day are considered safe for most patients.
   b. There is an increased risk of all-cause mortality at doses greater than 150 IU/day.
   c. Vitamin E, at recommended doses for dementia, can cause significant diarrhea and flatulence.
   d. Vitamin E, at any dose, has no effect on the INR.

9. A patient wishes to give a natural product to her mother who has been diagnosed with Alzheimer's dementia. Her daughter did not want to give her any more prescription drugs, because she believes they are all toxic and states her Mom is taking too many already. Her mother takes clopidogrel (an antiplatelet agent), amlodipine, simvastatin, and aspirin. The best product to recommend is:
   a. Ginkgo biloba
   b. Huperzine A
   c. Vitamin E
   d. None of the above

10. A patient is using donepezil. It is reasonable to recommend huperzine A concurrently.
   a. True
   b. False

Answers: 1-d; 2-a; 3-b; 4-a; 5-c; 6-d; 7-d; 8-b; 9-b; 10-b

REFERENCES

1. Product review. Ginkgo biloba. Available at www.ConsumerLab.com. Accessed August 16, 2005.
2. Ilieva I, Ohgami K, Shiratori K, et al. The effects of Ginkgo biloba extract on lipopolysaccharide-induced inflammation in vitro and in vivo. *Exp Eye Res*. 2004 Aug;79(2):181–7.
3. Ho GJ, Drego R, Hakimian E, et al. Mechanisms of cell signaling and inflammation in Alzheimer's disease. *Curr Drug Targets Inflamm Allergy*. 2005 Apr;4(2):247–56.
4. Pasinetti GM. From epidemiology to therapeutic trials with anti-inflammatory drugs in Alzheimer's disease: the role of NSAIDs and cyclooxygenase in beta-amyloidosis and clinical dementia. *J Alzheimers Dis*. 2002 Oct;4(5):435–45.
5. Cole GM, Morihara T, Lim GP, et al. NSAID and antioxidant prevention of Alzheimer's disease: lessons from in vitro and animal models. *Ann N Y Acad Sci*. 2004 Dec;1035:68–84.

6. Schmidt R, Schmidt H, Curb JD, et al. Early inflammation and dementia: a 25-year follow-up of the Honolulu–Asia Aging Study. *Ann Neurol.* 2002 Aug;52(2):168–74.

7. Hopfenmuller W. [Evidence for a therapeutic effect of Ginkgo biloba special extract. Meta-analysis of 11 clinical studies in patients with cerebrovascular insufficiency in old age]. German. *Arzneimittelforschung.* 1994;44:1005–13.

8. Kanowski S, Herrmann WM, Stephan K, et al. Proof of efficacy of the Ginkgo biloba special extract EGb 761 in outpatients suffering from mild to moderate primary degenerative dementia of the Alzheimer type or multi-infarct dementia. *Pharmacopsychiatry.* 1996;29:47,56.

9. Kleijnen J, Knipschild P. Ginkgo biloba. *Lancet.* 1992;340:1136–9.

10. Le Bars PL, Katz MM, Berman N, et al. A placebo-controlled, double-blind, randomized trial of an extract of Ginkgo biloba for dementia. North American EGb Study Group. *JAMA.* 1997;278:1327–32.

11. Wettstein A. Cholinesterase inhibitors and Ginkgo extracts—are they comparable in the treatment of dementia? Comparison of published, placebo-controlled efficacy studies of at least six months duration. *Phytomedicine.* 2000;6:393–401.

12. DeFeudis FV. *Ginkgo biloba Extract (EGb 761): Pharmacological Activities and Clinical Applications.* Paris, France: Elsevier Science; 1991:143,146.

13. Arenz A, Klein M, Fiehe K, et al. Occurrence of neurotoxic 4'-O-methylpyridoxine in ginkgo biloba leaves, ginkgo medications and Japanese ginkgo food. *Planta Med.* 1996;62:548–51.

14. Yin OQ, Tomlinson B, Waye MM, et al. Pharmacogenetics and herb–drug interactions: experience with Ginkgo biloba and omeprazole. *Pharmacogenetics.* 2004;14:841–50.

15. Fong KC, Kinnear PE. Retrobulbar haemorrhage associated with chronic Gingko biloba ingestion. *Postgrad Med J.* 2003;79:531–2.

16. Hauser D, Gayowski T, Singh N. Bleeding complications precipitated by unrecognized Gingko biloba use after liver transplantation. *Transpl Int.* 2002;15:377–9. Epub 2002 Jun 19.

17. Engelsen J, Dalsgaard N, Winther K. The health care products Coenzyme Q10 and Ginkgo biloba do not interact with warfarin. *Thromb Haemost.* 2001(Suppl);Abstract No. P796.

18. Ang-Lee MK, Moss J, Yuan CS. Herbal medicines and perioperative care. *JAMA.* 2001;286:208–16.

19. Zhang SL. [Therapeutic effects of huperzine A on the aged with memory impairment]. Chinese. *New Drugs and Clinical Remedies.* 1986;5:260–2.

20. Zhang RW, Tang XC, Han YY, et al. Drug evaluation of huperzine A in the treatment of senile memory disorders. *Zhongguo Yao Li Xue Bao*. 1991;12:250–52. Chinese; English abstract.

21. Wang R, Tang XC. Neuroprotective effects of huperzine A. A natural cholinesterase inhibitor for the treatment of Alzheimer's disease. *Neurosignals*. 2005;14(1–2):71–82.

22. Wang H, Tang XC. Anticholinesterase effects of huperzine A, E2020, and tacrine in rats. *Zhongguo Yao Li Xue Bao*. 1998;19:27–30.

23. Sano M, Ernesto C, Thomas RG, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study. *N Engl J Med*. 1997;336:1216–22.

24. Klatte ET, Scharre DW, Nagaraja HN, et al. Combination therapy of donepezil and vitamin E in Alzheimer disease. *Alzheimer Dis Assoc Disord*. 2003;17:113–6.

25. Lonn E, Bosch J, Yusuf S, et al. HOPE and HOPE-TOO Trial Investigators. Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial. *JAMA*. 2005;293:1338–47.

26. Miller ER 3rd, Pastor-Barriuso R, Dalal D, et al. Meta-analysis: High-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med*. 2005;142:37–46.

CHAPTER 3

Migraine

Karen Shapiro and Jack J. Chen

The World Health Organization now recognizes migraine as one of the most disabling medical conditions. There are 50 million Americans who suffer from chronic, severe headaches. Migraine is the most common type and is often misdiagnosed. Patients with migraine report an average of one to five attacks per month of moderate-to-severe pain, usually unilateral and accompanied by other symptoms, such as gastrointestinal upset, photophobia, and phonophobia.[1] Many patients would benefit from a combination of acute therapy (to treat attacks when they occur) and prophylactic therapy (to reduce the frequency of attacks). The natural products that are efficacious in treating an acute attack are caffeine, available in over-the-counter migraine products such as Excedrin® migraine, and magnesium, which is occasionally used in the acute care setting. Triptan agents, along with other classes of drugs, are used to resolve the acute attack. Common natural products used for prophylaxis include feverfew, butterbur, riboflavin, coenzyme Q10 (coQ10), and magnesium.

KEY POINTS

- Studies of feverfew in migraine prophylaxis offer conflicting results, which may be attributable to poor product quality.
- Preliminary data support the use of butterbur in migraine prophylaxis.
- Riboflavin is another name for vitamin B2, an essential nutrient in energy production.
- Riboflavin, in relatively high doses, may be useful for migraine prophylaxis.
- Riboflavin is inexpensive and well tolerated.
- Coenzyme Q10 may be useful for migraine prophylaxis.
- Magnesium is being studied for migraine prophylaxis and may provide benefit.
- Magnesium, in the recommended doses, is inexpensive and is well tolerated with the exception of mild gastrointestinal upset and loose stools in 20% of patients.
- Feverfew, butterbur, riboflavin, coenzyme Q10, and magnesium require larger, well-designed clinical trials in order to establish efficacy for migraine prophylaxis.

FEVERFEW

Feverfew (*Tanacetum parthenium*) is a perennial herb native to Southeastern Europe. According to Plutarch, the herb was named parthenium because it supposedly saved the life of a masonworker who fell from the roof of the Parthenon as it was being built. The plant is also known as midsummer daisy. This pretty plant has flowers with yellow center disks and white petals. The aromatic leaves have been used traditionally for inflammatory conditions

PRODUCT	DOSAGE	EFFECT	SAFETY CONCERNS
Feverfew	80 to 100 mg/day	Conflicting study data; may decrease frequency by 15% to 24%; 4 to 8 weeks for benefit	• May have additive risk with antiplatelets and anticoagulants • May decrease concentration of some medications • Avoid chewing leaves • Do not discontinue abruptly • Do not use in pregnancy or lactation
Butterbur	75 mg twice daily	May decrease frequency by 48% to 60%; may take 16 weeks for maximum benefit	• Use pyrrolizidine-free extract • Avoid use in liver disease
Riboflavin	400 mg/day	May decrease frequency by > 50%; allow at least 4 weeks for benefit	• Safe at recommended doses, including in pregnancy
Coenzyme Q10	100 mg three times daily	May decrease frequency by 46% to 50%; allow at least 4 weeks for benefit	• Use caution with certain drugs; see text
Magnesium	600 mg/day	May decrease frequency by ~40%; allow at least 4 weeks for benefit	• Safe at recommended doses, including in pregnancy • Can cause loose stools

and headaches. Currently, the most common use of feverfew is migraine prophylaxis.

Feverfew

The mechanism of action for feverfew in migraine prophylaxis remains unclear. Parthenolide, the principal sesquiterpene lactone, has been studied extensively as the proposed active ingredient. However, one study looking at a concentrated extract of parthenolide found no benefit for prevention of migraine.[2] It seems more likely that some combination of feverfew constituents is contributing to an antimigraine effect. This effect may be due to an inhibition of serotonin release, prostaglandin synthesis, and platelet aggregation.[3,4] Feverfew components might also prevent vascular muscle contraction.[5] Parthenolide may, however, be useful as an anti-inflammatory and chemotherapeutic agent.[6,7]

Studies of feverfew in migraine prophylaxis offer conflicting results. Two randomized, placebo-controlled trials that used whole feverfew leaf found feverfew effective as a prophylactic agent. The onset of benefit was observed in 4 to 8 weeks.[8,9] Others found no benefit.[10,11] One of the two trials that found

PATIENT CASE

CAROL

Carol is a 28-year-old, 70-kg white female who complains of a severe, right-sided throbbing headache for the past 8 hours. The episode started with blind spots in both eyes, flashing lights, photophobia, nausea, vomiting, and a tingling feeling in the fingers of her left hand. These symptoms gradually subsided as the headache started, although the nausea persists. Carol usually uses sumatriptan for acute pain relief but ran out. She states this medication works fine and asks for a refill prescription. She uses the sumatriptan four or five times monthly.

Her doctor has been trying to find a daily medication she can tolerate to help reduce the headache frequency. She has tried propranolol, which made her tired, and divalproex sodium, which made her gain weight. She asks if there is a natural product that does not have side effects. She has heard about feverfew and asks if it works. "I'm desperate," she says, "to try something else. These headaches are killing me!"

efficacy reported a reduction in migraine frequency of 24%. In trials with this product and the other products presented here, a placebo reduces migraine frequency by approximately 15%, which makes the overall benefit for the active product less than 10%. Other products discussed later provide a greater reduction in migraine frequency. With feverfew, some of the variability in study results appears to be due to product variability. The only way to determine the actual benefit is to have well-designed trial data, which at present are not available.

Patients should be counseled to choose whole-leaf, encapsulated products, in dosages of 80 to 100 mg per day.

SAFETY CONSIDERATIONS/DRUG INTERACTIONS

Feverfew is tolerated better than the available prescription agents. There is a theoretical risk of additive antiplatelet or anticoagulant effects when using feverfew with drugs such as warfarin, aspirin, and clopidogrel. Patients using these combinations should be aware of a potential increased risk of bleeding and understand how to monitor for bleeding. There are preliminary data indicating that feverfew may inhibit hepatic enzymes, which would increase the concentration of substrate drugs. Chewing feverfew leaves can cause oral ulcers.[10] Feverfew products may contain little or no dried leaf.[12] Upon abrupt discontinuation of feverfew, patients may experience a "postfeverfew syndrome" characterized by anxiety, insomnia, joint stiffness, and rebound headaches. Feverfew should be not be taken by women who are pregnant or breastfeeding.

Choosing a reputable product is essential because product quality is variable. Feverfew is a member of the ragweed plant family and patients with allergies to this plant family (including chrysanthemums, marigolds, and daisies) should avoid this product.

BUTTERBUR

Butterbur grows in wet, marshy areas and along rivers in North America, parts of Asia, and Europe. It resembles rhubarb and is also called bog rhubarb. The leaves, rhizomes, and roots of butterbur contain the sesquiterpene compounds petasin and isopetasin.[5] These constituents inhibit leukotriene synthesis, which may also contribute to butterbur's antispasmodic and anti-inflammatory actions.[13,14]

Butterbur

Butterbur extracts contain other components that may contribute to efficacy, including flavonoids, tannins, and pyrrolizidine alkaloids.[15]

A standardized extract of butterbur has been used in randomized, placebo-controlled, double-blind clinical trials (Petadolex®, Weber & Weber International GmbH & Co., Germany.) This formulation reduced the frequency of migraines by 48% to 60%, along with a reduction in the intensity of existing migraines.[16,17] Butterbur also appears effective for allergic rhinitis.[18]

The benefit from this product increases with time. In one of the trials referenced previously, maximum benefit was not seen until the 16th week. A typical dose is 75 mg twice daily.[17]

Safety Considerations/Drug Interactions

Butterbur leaf and rhizome contain pyrrolizidine alkaloids, which are hepatotoxic and potentially carcinogenic.[19] Fortunately, these compounds can be safely removed. Consumers need to choose pyrrolizidine-free extracts. It is prudent to avoid all butterbur products, including pyrrolizidine-free formulations, in persons with liver disease. Side effects from the use of pyrrolizidine-free extracts are rare and consist primarily of mild gastrointestinal complaints.

Riboflavin

Riboflavin (vitamin B2) is an essential nutrient critical to the body's production of adenosine triphosphate (ATP), the main cellular energy source. Riboflavin is the precursor of flavin mononucleotide and flavin adenine dinucleotide, which are required for the activity of flavoenzymes involved in the electron transport chain. Riboflavin supplementation is thought to remedy a type of mitochondrial dysfunction which results in impaired oxygen metabolism. The impaired oxygen metabolism may be contributing to an increase in migraine frequency.

Riboflavin 400 mg was compared to placebo in 55 chronic migraine patients in a randomized, 3-month trial. Riboflavin was significantly superior to placebo in reducing the attack frequency ($p = 0.005$), headache days ($p = 0.012$), and migraine index ($p = 0.012$). Most of the participants in the treatment arm experienced more than a 50% reduction in migraine frequency. No serious adverse events were reported.[20] A second open-label study showed similar benefit.[21] Larger studies are required to provide a more definitive conclusion regarding benefit.

The Recommended Dietary Intake (RDI) for riboflavin is 1.1 mg/day for women and 1.3 mg/day for men.[22] Riboflavin deficiency is rare, except in alcoholics. The dosage typically used for migraine prophylaxis is 400 mg/day. A trial period should extend for at least 4 weeks. This dose is high compared to the RDI, but it is a safe daily intake.

SAFETY CONSIDERATIONS/DRUG INTERACTIONS

No toxic effects of riboflavin at doses of 400 mg/day have been reported. At present, the low cost (less than 30 cents/day) and tolerability of riboflavin suggest that it could be tried as a reasonable option. It is reasonable to recommend in pregnancy.

COENZYME Q10 (CoQ10)

CoQ10, also known as ubiquinone, is a naturally occurring antioxidant compound. The name of this supplement comes from the word ubiquitous, which means "found everywhere." Indeed, CoQ10 is found in every cell in the body. It plays a fundamental role in the mitochondria in energy production. The body normally produces sufficient CoQ10, although some medications such as statins may interfere with this process. CoQ10 levels in the body decline with age and certain disease states, including heart disease.

CoQ10 is used most commonly for congestive heart failure; however, the data for heart failure use are inconclusive. Data for migraine prophylaxis appear better, but the two available trials are small and only one is blinded and placebo-controlled. The other is open-label design.[23,24] In the open-label trial, mean reduction in migraine frequency was 55% at the end of 3 months. In the second trial, the reduction in migraine frequency was 46%. The dose used in the blinded, controlled trial was 100 mg three times daily and is the dose typically recommended for this indication.

SAFETY CONSIDERATIONS/DRUG INTERACTIONS

CoQ10 does not cause significant adverse events. Mild gastrointestinal events occurred in clinical trials, with similar frequency to the placebo groups. Concomitant administration of CoQ10 and the chemotherapy drug doxorubicin (Adriamycin®) should be avoided as CoQ10 can alter the metabolism of doxorubicin and increase the concentration of a potentially toxic metabolite. CoQ10 therapy, however, has been used to help prevent cardiac toxicities of doxorubicin, when used after the cessation of chemotherapy.

Cholesterol-lowering drugs such as simvastatin (Zocor®), lovastatin (Mevacor®) and gemfibrozil (Lopid®) may decrease plasma and tissue CoQ10 levels. It is unclear whether normalizing coenzyme Q10 levels via supplementation will benefit patients taking these statins or gemfibrozil. Pravastatin (Pravachol®) and atorvastatin (Lipitor®) do not lower coenzyme Q10 levels.[25] The beta-blockers propranolol and metoprolol may also inhibit coenzyme Q10-dependent enzymes and ultimately lower CoQ10 levels.

CoQ10 is structurally similar to vitamin K. Therefore, a procoagulant effect (resulting in a decreased international normalized ratio) when combined with warfarin has been suggested, but a small study found no interaction between CoQ10 and warfarin.[26]

MAGNESIUM

Magnesium is an essential nutrient found in significant quantities throughout the body and used for numerous purposes, including muscle relaxation, blood clotting, and the manufacture of ATP. In the ambulatory population, magnesium is used most commonly as a laxative and antacid. It is also used as a "natural" calcium channel blocker for hypertension.

Most people get adequate magnesium through the diet, although deficiencies in certain disease groups, including hypertension, diabetes, and migraine, may be underrecognized.[27,28] The RDI is 420 mg/day for males and 320 mg/day for females.[22]

In one double-blind study of 81 patients, supplementation with magnesium 600 mg/day reduced migraine frequency by 42%, compared to 16% in the placebo group.[29] Twenty percent of subjects using magnesium reported diarrhea and, less often, gastrointestinal upset. Two other smaller studies showed benefit. The first study involved 43 patients using magnesium 600 mg/day in a double-blind, crossover pilot study.[30] Similar to other studies, onset for effectiveness was 4 weeks. The second double-blind study involved 20 women with premenstrual migraine taking magnesium 360 mg/day. In patients taking magnesium, there was a decrease in the number of days with headache and a significant decrease in pain.[28] A reasonable magnesium dose to recommend is 600 mg/day, for at least a 4-week trial. All magnesium salts are absorbed fairly well, although the most common magnesium formulation, magnesium oxide, is thought to be less well absorbed than magnesium citrate.

SAFETY CONSIDERATIONS/DRUG INTERACTIONS

Magnesium can cause diarrhea (more accurately, loose stools), and to a lesser extent, gastrointestinal upset, particularly at these higher doses. With a larger daily intake it is reasonable to consider the risk of hypermagnesemia, which can produce fatal arrhythmias. Known cases of hypermagnesemia involved ingestion of much larger amounts than those proposed here, such as ingestion of large quantities of epsom salts or excessive quantities used in very young children.[31,32] In patients with significantly reduced renal function, this may be a more significant concern due to reduced elimination. Patients with heart disease should not take excessive doses of magnesium without consulting their physician due to a preexisting risk for arrhythmias. Quinolone antibiotics, such as ciprofloxacin, and tetracycline antibiotics should be taken

2 hours before or 4 hours after magnesium supplements. Patients need to choose a formulation that has been tested for lead content. Magnesium occurs naturally with small amounts of lead; however, some supplements contain unsafe amounts.[33] Magnesium, at this suggested dose, is safe in pregnancy.

PATIENT DISCUSSION

Prior to discussing an appropriate natural product for Carol, it should be noted that her prescription options for prophylaxis are not yet exhausted. She might find that other prescription agents are better tolerated. She may also benefit from a combination of medication and a nonpharmacologic intervention for migraine prophylaxis. Biofeedback and relaxation therapy both reduce the frequency of migraines by about 50%, which is roughly equivalent to propranolol and other prophylactic therapies.[34]

She should be counseled to record a migraine history and attempt to identify triggers, in the hope that the triggers could be avoided. Triggers include hormonal changes; weather patterns; bright, flashing, or fluorescent lights; foods such as chocolate, wine, cheese, and caffeine; aspartame; and patient-specific food sensitivities.[35]

Any of the other products presented here might be helpful. Since she is of childbearing age, an appropriate initial recommendation would be riboflavin or magnesium. At present, there are only small studies of all the popular migraine agents, but the studies for riboflavin, magnesium, and coenzyme Q10 are promising. Feverfew is the best-known natural product for migraine prophylaxis; however, the data to support the use of feverfew are contradictory. Feverfew is safe for most patients and if Carol wishes to try it, she should choose a product made from whole leaf prepared in a formulation she can swallow (i.e., she should not chew feverfew leaves.)

Interestingly, there has been a study of a combination product of magnesium, riboflavin, and feverfew that did not appear to offer benefit; however, the study design was poor.[36] If a patient wishes to combine any of the products discussed here, it would be prudent to suggest one agent at a time, so that efficacy of each individual agent can be assessed. If a patient receives benefit from two or more individual agents, a combination product might simplify the regimen.

SELF-ASSESSMENT

1. **Which is TRUE concerning feverfew:**
   a. Several large, randomized trials have demonstrated that feverfew reduces migraine frequency by 85%.
   b. Patients should be advised to chew whole-leaf product for best effect.
   c. Feverfew may increase bleeding risk in patients on anticoagulants.
   d. All of the above.

2. **Which of the following products is a member of the ragweed family?**
   a. Feverfew
   b. Magnesium
   c. Riboflavin
   d. Coenzyme Q10

3. **Which is the correct dose of feverfew to recommend in migraine prophylaxis?**
   a. 1 to 2 mg/day
   b. 80 to100 mg/day
   c. 0.2 mcg/day
   d. None of the above

4. **Which is TRUE concerning butterbur:**
   a. Preliminary data suggest that butterbur may reduce migraine frequency.
   b. Butterbur is typically dosed at 75 mg twice daily.
   c. Butterbur supplements must be pyrrolizidone-free.
   d. All of the above.

5. **Which is TRUE concerning riboflavin:**
   a. Riboflavin is vitamin B2.
   b. Riboflavin is important in the production of ATP.
   c. Riboflavin 400 mg/day may reduce migraine frequency.
   d. All of the above.

6. **Which is TRUE concerning riboflavin:**
   a. Riboflavin is very expensive.
   b. Riboflavin deficiency is common.
   c. Riboflavin is inexpensive and well tolerated.
   d. None of the above.

7. Which is TRUE concerning coenzyme Q10:
   a. It is also called ubiquinone.
   b. It is important in mitochondrial energy production.
   c. Endogenous levels decrease with aging.
   d. All of the above.

8. Which is TRUE concerning coenzyme Q10:
   a. It may increase blood glucose levels.
   b. It is difficult for most patients to tolerate at recommended doses.
   c. A product of good quality is hard to find.
   d. None of the above.

9. A patient wishes to try a natural product for migraine prophylaxis. She has diarrhea-predominant irritable bowel syndrome and liver disease (hepatitis B and C positive), from years of IV drug abuse. She reports ragweed allergy. Which of the following products is best to recommend?
   a. Magnesium
   b. Feverfew
   c. Riboflavin
   d. Butterbur

10. A reasonable trial period for natural products for migraine is 4 to 6 weeks, except for butterbur, which may take longer.
   a. True
   b. False

Answers: 1-c; 2-a; 3-b; 4-d; 5-d; 6-c; 7-d; 8-d; 9-c; 10-a

REFERENCES

1. Silberstein SD. Migraine. *Lancet*. 2004 Jan 31;363(9406):381–91. Review.
2. de Weerdt CJ, Bootsma HPR, Hendriks H. Herbal medicines in migraine prevention. Randomized double-blind placebo-controlled crossover trial of a feverfew preparation. *Phytomedicine*. 1996;3:225–30.
3. Hwang D, Fischer NH, Jang BC, et al. Inhibition of the expression of inducible cyclooxygenase and proinflammatory cytokines by sesquiterpene lactones in macrophages correlates with the inhibition of MAP kinases. *Biochem Biophys Res Commun*. 1996 Sep 24;226(3):810–8.
4. Heptinstall S, White A, Williamson L, et al. Extracts of feverfew inhibit granule secretion in blood platelets and polymorphonuclear leucocytes. *Lancet*. 1985 May 11;1(8437):1071–4.
5. Barsby RW, Salan U, Knight DW, et al. Feverfew extracts and parthenolide irreversibly inhibit vascular responses of the rabbit aorta. *J Pharm Pharmacol*. 1992;44:737–40.

6. Guzman ML, Rossi RM, Karnischky L, et al. The sesquiterpene lactone parthenolide induces apoptosis of human acute myelogenous leukemia stem and progenitor cells. *Blood*. 2005 Jun 1;105(11):4163–9. Epub 2005 Feb 1.

7. Sweeney CJ, Mehrotra S, Sadaria MR, et al. The sesquiterpene lactone parthenolide in combination with docetaxel reduces metastasis and improves survival in a xenograft model of breast cancer. *Mol Cancer Ther*. 2005 Jun;4(6):1004–12.

8. Murphy JJ, Heptinstall S, Mitchell JR. Randomized, double-blind, placebo-controlled trial of feverfew in migraine prevention. *Lancet*. 1988;2:189–92.

9. Palevitch D, Earon G, Carasso R. Feverfew (*Tanacetum parthenium*) as a prophylactic treatment for migraine—a double-blind, placebo-controlled study. *Phytotherapy Res*. 1997;11:508–11.

10. Johnson ES, Kadam NP, Hylands DM, et al. Efficacy of feverfew as prophylactic treatment of migraine. *Br Med J* (Clin Res Ed). 1985;291:569–73.

11. Vogler BK, Pittler MH, Ernst E. Feverfew as a preventive treatment for migraine: a systematic review. *Cephalalgia*. 1998;18:704–8.

12. Jellin JM, Gregory PJ, Batz F, et al. Natural Medicines Comprehensive Database. Therapeutic Research Faculty. Stockton CA; 2005. Available at www.naturaldatabase.com. Accessed August 6, 2005.

13. Bickel D, Röder T, Bestmann HJ, et al. Identification and characterization of inhibitors of peptido-leukotriene synthesis from *Petasites hybridus*. *Planta Med*. 1994;60:318–22.

14. Thomet OAR, Wiesmann UN, Schapowal A, et al. Role of petasine in the potential anti-inflammatory activity of a plant extract of *Petasites hybridus*. *Biochem Pharmacol*. 2001;61:1041–7.

15. Jellin JM, Gregory PJ, Batz F, et al. Natural Medicines Comprehensive Database. Therapeutic Research Faculty. Stockton CA; 2005. Available at www.naturaldatabase.com. Accessed July 27, 2005.

16. Diener HC, Rahlfs VW, Danesch U. The first placebo-controlled trial of a special butterbur root extract for the prevention of migraine: reanalysis of efficacy criteria. *Eur Neurol*. 2004;51:89–97.

17. Lipton RB, Gobel H, Einhaupl KM, et al. Petasites hybridus root (butterbur) is an effective preventive treatment for migraine. *Neurology*. 2004;63:2240–4.

18. Lee DK, Gray RD, Robb FM, et al. A placebo-controlled evaluation of butterbur and fexofenadine on objective and subjective outcomes in perennial allergic rhinitis. *Clin Exp Allergy*. 2004;34:646–9.

19. Brown DJ. Standardized butterbur extract for migraine treatment: a clinical overview. *HerbalGram*. 2003;58:18–9.

20. Schoenen J, Lenaerts M, Bastings E. High-dose riboflavin as a prophylactic treatment of migraine: results of an open pilot study. *Cephalalgia*. 1994;14:328–9.

Natural Products

A Case-Based Approach for Health Care Professionals

Karen Shapiro

Consumers' use of echinacea, ginseng, ginkgo, and other "alternative" remedies is skyrocketing. By 2002 nearly 19% of Americans were using natural products weekly, with the greatest use in people over age 65. Today, forward-thinking clinicians recognize the need to know more about natural products. What are the key benefits of natural products in treating common conditions? What are the risks? Yet many health care providers feel uncertain about guiding patients in the choice of these products.

Using patient case scenarios, *Natural Products: A Case-Based Approach for Health Care Professionals* helps you master key information by providing product details and safety considerations for products proven helpful in treating 14 common conditions. Whether you're a practitioner seeking practical know-how or a student building a foundation of knowledge, you'll appreciate the text's user-friendly format, product charts, summaries, and photos.

Highlights

- A chapter each on 14 common conditions, from cold and flu to erectile dysfunction, menopause, and migraine. Each chapter demonstrates the role of natural products via patient cases and covers the commonly used natural products, their dosage and effects, and safety considerations/drug interactions.
- Introductory chapter on the role of natural products, including product selection advice and patient care tips.
- Learning aids such as product tables providing key details quickly, photos to aid product identification, listings of key points to remember, and self-assessment questions.
- Extensive references documenting the scientific evidence for use or avoidance of each product.

About the Author

Karen Shapiro, PharmD, BCPS, is a clinical pharmacist in the Department of Medicine at Rancho Los Amigos National Rehabilitation Center in Los Angeles and an adjunct assistant professor at the University of Southern California School of Pharmacy and the University of Florida Working Professional Doctor of Pharmacy Program. A member of Medscape's "Ask the Expert" pharmacotherapy panel, Dr. Shapiro has published in the areas of natural products, geriatric pharmacotherapy, and pain management.

American Pharmacists Association®
Improving medication use. Advancing patient care.
APhA

ISBN 1-58212-069-2
9 781582 120690