THE ANCIENT HISTORY AND MODERN REGULATION OF MEDICINAL HERBS

ANCIENT HERBAL HISTORY

Herbal medicine predates written history. Otzi the Iceman was discovered in 1991 on a mountaintop in the Ötztal Alps with a satchel full of medicinal herbs. He was carrying birch fungus 5300 years ago, which is now known to have anti-inflammatory, antiparasitic, and antibacterial properties. The remains of Otzi suggest he had arthritis and intestinal parasites. Was this mere coincidence?

Modern civilization has inherited a wealth of herbal literature from past centuries. The Sumerians wrote lists of herbs on clay tablets as far back as 3000 BCE. Further east around the same time, Shen Nung wrote Pen Ts’ao or Shennong Ben Cao Jing, a list of herbs that is most likely a compilation of an even older oral tradition of Chinese herbalism. A more comprehensive Chinese book of medicine, the Huangdi Neijing, was written around 250 BCE. The Kahoun Papyrus on gynecological disease and the Papyrus Ebers, both from ancient Egypt, date back to 1950 BCE and 1500 BCE, respectively. The latter included a broad range of remedies, one example being the use of elderberry for treating diabetes, an application that is now supported by scientific research.

Greeks and Romans have records of using herbs a millennium or two later through the work of Dioscorides (40–90 CE) and Claudius Galen (131–200 CE), from whom the herbal term “galenicals” is derived and who formulated the materia medica texts that continued to be referenced for the next 1500 years. Iranian physician Ibn Sina aka Avicenna (980–1037 CE) compiled The Canon of Medicine, which was widely used in Europe during the 11th and 12th centuries. Herbal knowledge was preserved in monasteries during the Middle Ages of Europe. Perhaps best known from this time is Hildegard von Bingen, a 12th-century Benedictine nun and polymath who wrote on medicinal herbs, among other things. All these works became more widely distributed with the invention of the printing press in 1439, and herbal healing entered into widespread use by lay practitioners. Meanwhile, over in the New World, the Aztecs were found by the conquering Spanish to be expert herbalists. In 1552, the Badianus Manuscript entitled Libellus de Medicinalibus Indorum Herbis (“Little Book of the Medicinal Herbs of the Indians”) was compiled as a list of herbs that had been used by the Aztecs as medicines for centuries.

With such extensive herbal literature surviving the millennia and continuing to be applied currently, and with modern scientific research verifying the efficacy of a vast number of traditional herbal usages, the big question is, “How did they know?” Was it just trial and error over hundreds of years or was it something more mysterious? Medicinal herbs are known to have come into use through a few different approaches. Initially, there was a recognition that adding culinary herbs to foods bestowed upon the foods an increase in safety margin largely due to the antimicrobial effects of the essential oil constituents of the herbs. Another herbal application theory is called “the doctrine of signatures.” According to this theory, every herb has its own “sign.” The appearance of the plant and its color, scent, or living environment indicate its medicinal use. Walnuts that look like the brain are good for the brain.
Herbs used to cure jaundice such as marigold and dandelion have yellow flowers. Hard-barked trees are good for bones. Willow, with its flexibility, was identified as being good for joints. Astrology was another means for deciphering the applications of herbs. Then, in the late 16th century came experimental science. A rift evolved between the more scientifically inclined medical practitioners and those who continued to look at plants or the stars. The scientific method was born and continues to be the guiding light for the field of medicine. It is fascinating that the scientific method appears to be increasingly validating many of the practices derived through the more ancient methods of gaining knowledge.

**LEGITIMIZATION OF MEDICINAL HERBS IN THE 20TH CENTURY**

Although medical herbalism has retained strong thread of continuity in many regions of the world, Western civilization took a time-out from herbalism with the introduction of pharmaceuticals in the late 19th and early 20th centuries. It was later in the 20th century that ancient history and modern science began to find common ground, and with this common ground came the need to proceed cautiously and systematically. In both Europe and the United States, collective agencies arose to address this need.

**European Authentication of Herbal Therapy: German Commission E, ESCOP, and BHP**

The German Commission E is a scientific advisory board of the “Bundesinstitut für Arzneimittel und Medizinprodukte” formed in 1978. The commission provides scientific expertise for the approval of substances and products previously used in traditional, folk, and herbal medicine. The commission became known beyond Germany in the 1990s for compiling and publishing monographs evaluating the safety and efficacy of 380 herbs for licensed medical prescribing in Germany. The monographs were published between 1984 and 1994 and have not been updated since then; however, they are still considered to hold validity. In 1998, Mark Blumenthal translated the monographs into English and published *The Complete German Commission E Monographs: Therapeutic Guide to Herbal Medicines*.

The European Scientific Cooperative on Phytotherapy (ESCORP) was founded in 1989 as an umbrella organization over the national European phytotherapy associations. Like the Commission E in Germany, a working group is assigned to ESCOP for the development of consistent assessment criteria for herbal medicines. Its members come from universities and professional societies of numerous European countries. The collected information is published in the ESCOP Monographs.

British Herbal Pharmacopoeia was developed in 1983 by the British Herbal Medical Association. The second edition was published in 1996 and provides quality standards for 169 different herbs. The *British Herbal Compendium* consists of Volumes 1 and 2 that were published by the British Herbal Medical Association in 1992 and 2006, respectively. Volume 1 offers scientific information on medicinal herbs for which quality standards are defined in the revised British Herbal Pharmacopoeia. It covers about half of the plant drugs in BHP 1996 and the others are covered in Volume 2. Volume 2 provides concise monographs that summarize and review the evidence for many medicinal herbs.

**Authentication of Medicinal Herbs in the United States**

**United States Pharmacopoeia (USP)**: The original attempt in the United States to systemize and authenticate medicinal herbs was through monographs written in 1820 to improve the safety of the available drugs of the time. The USP was developed originally by 11 physicians to protect patients from poor-quality medicines. Since then, the USP has developed monograph standards for more than 900 nutritional and dietary supplement products. When the USP was formed in the early 19th century, many new plants were being discovered and used to produce drug components for patient treatment. Until publication of the first USP, there was no standardized information regarding plant processing, such as which part of the plant or which method of extraction of plant material should be
used. The first edition of the USP mainly focused on drugs of plant origin, many of which were native to the United States. In 1975, the USP combined with the National Formulary to become the USP-NF. By 2020, the USP-NF had evolved into more than 5000 monographs for finished drug products. As modern pharmacotherapeutics took over, medicinal herbs fell into the background and were consequently given their own platform in the Herbal Medicines Compendium (HMC). Between 2014 and 2020, 57 monographs were finalized and made freely available online, with numerous other monographs in the works (See Appendix II). The HMC monographs provide standards for ingredients used in herbal medicines. Each monograph contains general information including the definition of the herbal ingredient relative to the monograph title and specifications of tests for critical quality attributes of the herbal ingredient and analytical test procedures.

American Herbal Pharmacopoeia (AHP): The AHP began developing qualitative and therapeutic monographs in 1994, with the intention of providing the most comprehensive and critically reviewed body of information on herbal medicines in the English language. As of 2020, there are 40 completed monographs, with the goal of 300 monographs on botanicals, including many of the Ayurvedic, Chinese, and Western herbs most frequently used in the United States. In 2020 a complete set of colorful hard-copy monographs could be purchased from AHP for $1278.40.

Federal Regulation of Medicinal Herbs in the United States

DSHEA and CGMP Legislation: In the late 1980s and early 1990s, Congress was considering several bills that would tighten regulations regarding dietary supplement labeling. After backlash from the dietary supplement industry, US senators Orrin Hatch (R-Utah) and Tom Harkin (D-Iowa) introduced the “Dietary Supplement Health and Education Act” (DSHEA) in 1994, which was subsequently signed into law by President Bill Clinton. The act defined the term “dietary supplement” to mean a product intended to supplement the diet that bears or contains one or more dietary ingredients, including “a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total dietary intake, or a concentrate, metabolite, constituent, extract, or combination of any of the aforementioned ingredients.” Under the act, any supplements that were marketed in the United States before 1994 did not require FDA approval. Those marketed after 1994 were designated New Dietary Ingredients and required review by the FDA prior to their marketing. The act stipulated that all dietary supplements be labeled as such, and that they could not be approved or authorized for investigation as new drugs, antibiotics, or biologics, unless they were marketed as food or dietary supplements before such approval or authorization. The act stipulated that each supplement be labeled with quantity of contents, serving size, percent daily value if appropriate, list of ingredients in descending order, plant parts used, safety information, and most importantly a disclaimer if the supplement bore a claim to affect the structure or function of the body, a claim of general well-being, or a claim of a benefit related to a classical nutrient deficiency disease. The disclaimer was to state, “This statement has not been investigated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.” DSHEA allowed the option for manufacturers to add information regarding quality assurance to the label. After the passage of DSHEA, the dietary supplement market grew rapidly, and access to these products expanded to supermarkets and online shopping. Alarm bells started to sound that the natural supplement industry was making huge profits without reasonable safety oversight. To address this concern, the FDA created a new set of current good manufacturing practices (CGMP) in 2007 that applied to the manufacturers of dietary supplements. The CGMP was phased in over 3 years and backed by regular inspections. The CGMP requires manufacturers to demonstrate clean hygienic manufacturing areas with controlled environmental conditions; avoidance of cross-contamination from adulterants and
allergens; clearly defined, validated, and documented manufacturing processes; product verification including quality and quantity; adequate training; tracking of batches; safe and reliable distribution methods; the existence of a recall system; and investigation and follow-up on any complaints received. Health care practitioners who directly provided supplements to their patients were excluded from CGMP requirements due to presumption of adequate training in the professional practice and their individualized patient-provider relationship.

**NCCAM and NCCIH:** Coincident with the legislation of the US Congress to better regulate the dietary supplement industry, Congress passed legislation in October 1992 to establish an office in the National Institutes of Health (NIH) to investigate and evaluate promising unconventional medical practices. This office was originally named the Office of Alternative Medicine (OAM). Six years later the National Center for Complementary and Alternative Medicine (NCCAM) was established in its place, allowing it independent status within the NIH.

In 1999 the Consortium for Advancing Research on Botanical and Other Natural Products (CARBON) Program was initiated, establishing two Botanical Dietary Supplement Research Centers (BDSRC). The purpose of the CARBON Program has been to promote research on the safety, effectiveness, and mechanisms of action of botanical dietary supplements that have a high potential to benefit human health, and to support the development of methods and resources to enhance the progress of this research. Part of the work of CARBON has been the establishment of a Natural Products Nuclear Magnetic Resonance Open Data Exchange to create open access to natural product chemical structure data.

NCCAM awarded its first research grant in 1999 and established CAM on PubMed in 2001. In May 2004 NCCAM announced its findings from a comprehensive survey on American adults’ use of complementary health approaches: 36% of US adults aged 18 years and older were using some form of CAM. In 2007, a survey showed that US adults had spent $33.9 billion out-of-pocket on visits to complementary health practitioners and on purchases of complementary health products, classes, and materials. In 2014 the NCCAM was renamed the National Center for Complementary and Integrative Health (NCCIH). It maintains the research-based website noted in Appendix II. In 2018 NCCIH released its first mobile app, HerbList, which provides science-based information on herbs and herbal products.

**RISING DEMAND FOR MEDICINAL HERBS IN THE UNITED STATES: IMPACT OF DRUG PRICES ON HERBAL POPULARITY**

In 1997, during roughly the same timeframe as the enactment of DSHEA and development of the NCCAM, the FDA eased up on a rule obliging pharmaceutical companies to offer a detailed list of side effects in their advertisements. This rule was followed by a proliferation of direct-to-consumer pharmaceutical advertisements. Coincidentally, drug price increases began to outpace inflation shortly thereafter. From 2000 through 2019 the AARP Public Policy Institute reported that drug price increases had consistently exceeded inflation (Schondelmeyer and Purvis). In 2006 the AARP reported that the cost of brand-name prescription drugs had outpaced the rate of inflation for the sixth year in a row. Prices had risen 40% on average over the preceding 6-year period, compared to a 17% rise through inflation over the same period. The report noted that the average price that drug makers charged wholesalers and other direct purchasers had increased 6% in 2005. Inflation over the same time had risen 3.4%. That same year, the FDA launched the Unapproved Drugs Initiative (UDI), which took many older “grandfathered” drugs off the market, giving exclusive rights for sales of those drugs to pharmaceutical companies that were willing to jump through the FDA hoops for approval. Using the high costs of obtaining approval for these older drugs as justification, the participating companies increased the prices of the revamped drugs by as much as 100-fold. As for the high costs of obtaining approval, nearly 90% of drugs that received FDA approval through the UDI were supported by literature reviews or bioequivalence studies rather than through new clinical trial evidence (Gupta et al.).
By 2019, even as the US government had begun investigating ways to slow rising drug prices, CBS News reported that manufacturers had hiked prices on 3400 drugs at an average increase of five times that of inflation. The report noted that four out of five Americans believed the cost of prescription drugs was unreasonable and about one in three patients indicated they were skipping prescription medicine because of the cost (CBS News).

Such are the forces that drive the need for increasing knowledge and safety in the natural supplement industry. For a patient looking at adding a new medication to his or her diabetes regimen, the $500–$1000 per month price tag on a newer drug becomes a figuratively bitter pill to swallow when there is an equally effective and reliable herbal product or natural supplement available online for consistently less than $20 per month. Considering the widespread availability, scientific evidence, improved quality, and basic affordability of natural supplements, it is not surprising that the 2019 Council for Responsible Nutrition Consumer Survey on Dietary Supplements revealed the highest overall dietary supplement usage to date, with 77% of Americans reporting they consume dietary supplements and 81% of adults aged 35–54 years reporting usage of dietary supplements. According to the American Botanical Council’s 2019 Herb Market Report, consumers in the United States spent an estimated $9.602 billion on herbal dietary supplements in 2019, an 8.6% increase in total US sales from 2018. It appears that the economics of health care in the United States are driving an increasing interest in and use of dietary supplements, a trend that is likely to continue into the foreseeable future.

REFERENCES