

CHAPTER 2

MEDICINAL PLANTS AND TOMORROW'S PHARMACY

An American perspective

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Abstract. Medicinal plants were among the first pharmaceuticals used in America, but the Flexner report in 1910, conventional drug introduction throughout the first half of the 20th century, and aggressive action by the FDA during the 1950s and 1960s to eliminate medicinal treatments for which no safety or efficacy data were available, essentially caused the abandonment of crude medicinal plant products for health care in America. Beginning mostly in the 1970s, however, social and political changes re-introduced the therapeutic benefits of medicinal plants to Americans seeking alternative health care. Although concerns about safety and efficacy are still issues with medicinal plants, the passage of the Dietary Supplement Health and Education Act (DSHEA) in 1994 ensured Americans access to an array of medicinal plant products and encouraged research into the pharmacological activity of medicinal plant materials. Based on current trends of prescription-drug costs and consumer desires for natural health-care products, American pharmacies of the future may well support both conventional and alternative medicine systems, enabling the consumer and the medical practitioner to choose the best medicine for the medical condition.

Keywords: health care; herbs; history; pharmaceuticals

Pharmaceuticals for early American health care came from the wide array of healing compounds produced in plants as secondary metabolites. Historically, the importance of plants as a source of drugs can be implied from close plantings of medicinal plant materials beside the home within easy reach of the homemaker for use in treatment of ailments. Indeed, plantings of medicinal herbs were fairly commonplace near homes and medical facilities in America until the early part of the 20th century (Weishan 1999). As evidenced by medical-school curricula in the 1800s, herbalists, midwives and physicians of the 19th and early 20th century were specially trained in the use of medicinal plants as pharmaceuticals. A number of books detailing the therapeutic properties of medicinal plants were also available to the public (Buffum et al. 1905, p. 981-1142; Corish 1938, p. 1145-1232; Richardson et al. 1905, p. 781-833), suggesting that the use of medicinal plants in the treatment of afflictions was most likely familiar to everyone.

The early *materia medica* of the United States consisted of plants the colonists

brought with them from Europe and American species that had been used for healing by Native Americans (Hoffman 1964; Kavasch and Baar 1999). In the development of patent medicines, the pharmacist and writer, John Uri Lloyd, included in his formulae both imported and native medicinal plants (Lloyd and Lloyd 1884-1887; Lloyd 1911). Medicinal preparations and medicinal plants were included in pharmaceutical publications through the early 1900s, and the 1918 edition of the U.S. Dispensatory included nearly 100 native plant species (Remington and Wood 1918). Interestingly, many of the native American species, including black cohosh (*Actaea racemosa*), echinacea (*Echinacea* spp.), goldenseal (*Hydrastis canadensis*), and cranberry (*Vaccinium macrocarpon*), in this early issue of the dispensatory have become popular herbal remedies in the U.S. and abroad (Blumenthal 2005).

Commercialization of medicinal plants into cure-all, patent medicines during the late 1800s created a populace suspicious about medicinal formulae made from natural products and may explain the hesitancy of some to accept claims of medicinal plants as valuable pharmaceuticals. With the pharmaceuticals used medical care generally lacking any type of meaningful standardization until after 1910, a wide variety of practitioners, some completely lacking in integrity, dispensed a wide variety of medicinal concoctions, frequently sold to an unsuspecting public through travelling medicine shows that touted miracle cures for everything from neuralgia and constipation to obesity and hair loss (Jayne 1883). Small booklets published by mail-order drug companies and made to appear 'scientific' advertised to the public the supposed cures associated with a company product (Figure 1). Such false claims connected to unscrupulous practitioners and

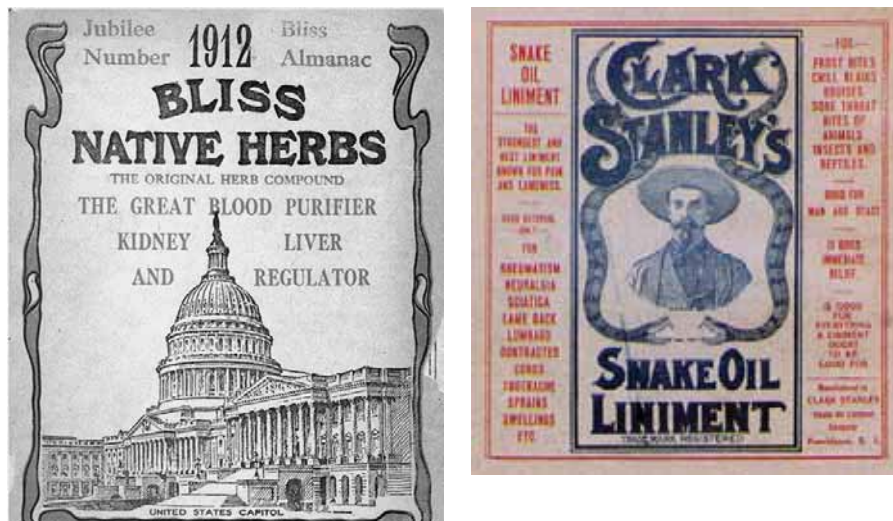


Figure 1. Cure-alls of the past (left: picture taken of booklet cover; right: from National Library of Medicine). Images from the History of Medicine

various companies eventually led to the development of standards in the practice of medicine.

A significant challenge to the use of botanical medicines in the U.S. was the Flexner Report of 1910 (Flexner 1910) (Figure 2). Commissioned by the American Medical Association and the Carnegie Foundation and written by Abraham Flexner, this report, which strongly influenced medical care in the U.S., suggested that only trained physicians should be allowed to prescribe medicines. The combined effects of the Flexner Report on the disuse of medicinal plants in medical practices and the rise in political power of the American Medical Association (A.M.A.), first formed in 1847, were tremendous. Within five years, the majority of schools specializing in botanical medicine in the country had closed, and within 28 years all schools that taught what is now considered complimentary or alternative medicine had closed, leaving only A.M.A.-approved schools in operation (Craker 2003; Griggs 1981). The use of plant medicines became unfashionable in an industrializing U.S. during the early 20th century with new thoughts and new, chemically based medicines for the new century.

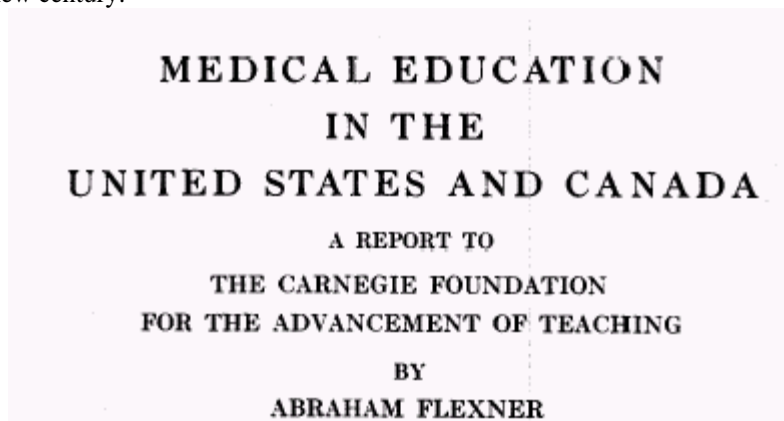


Figure 2. Cover of the Flexner report submitted in 1910

The health of people improved through the early 1900s by the recognition of micro-organisms as disease agents, the development sanitation procedures that prevented infections, and the formulation of sulphur drugs that fought infections. Vaccines for the prevention of tetanus, yellow fever, diphtheria and other diseases followed in the 1920s, and the potential of antibiotics was recognized after the discovery of penicillin in 1928 (marketed in 1942) (Table 1). The public, however, was still not protected from harmful or worthless products. Only after a toxic solvent (ethylene glycol) used as a sweetener in the manufacture of a sulphur drug (Elixir Sulfanilamide) resulted in the death of more than 100 people (mostly children) (National Academy of Science 2004, p. 22-23), did the U.S. Congress pass the Food, Drug, and Cosmetic Act of 1938. This law, which legally mandated quality and identity standards for foods, drugs, cosmetics and medical devices, prohibited false therapeutic claims and enabled government inspection of manufacturing facilities

and regulation of product advertising.

Table 1. *Some pharmaceutical innovations*

Year ¹	Therapeutic	Drug type	Drug
1785	Inotropic agent	Cardioglycoside	Digitoxin
1796	Smallpox vaccine	--	--
1803	Analgesic	Narcotic	Morphine
1867	Antiseptic	Phenol	Carbolic acid
1884	Analgesic	Alkaloid	Phenazone
1910	Antisymphilitic	Arsenical	Salversan
1935	Bactericide	Sulfonamides	Sulfamidochrysoidine
1942	Bactericide	Antibiotic	Penicillin
1987	Recombinant DNA	Hormone	Humulin

¹ Modified from Achilladelis (1999)

The value and protective strength of the 1938 law (along with subsequent amendments) and the Food and Drug Administration (FDA) in regulating pharmaceuticals was fully recognized by the thalidomide tragedy of the late 1950s and early 1960s, in which pregnant women in several countries that allowed thalidomide prescriptions (used for the treatment of morning sickness) gave birth to deformed babies (CERHR 2002). Because the FDA prevented the use of the thalidomide in the U.S., American babies were not affected and the FDA gained considerable political power in regulating American medicine. Following success against thalidomide and the passage of the Drug Amendments to the Food, Drug, and Cosmetic Act in 1962, the FDA required all manufacturers marketing a drug to submit proof on the safety and effectiveness of the drug, beginning an examination on the safety and health claims of several medicinal products. In this group of products were medicinal plants, many of which had been safely used for thousands of years, but for which no scientific proof of safety or efficacy existed. For these reasons, medicinal plants and medicinal plant extracts were essentially declared worthless and/or potentially harmful and FDA agents began raiding stores and manufacturing facilities that sold or processed medicinal plant products to stop sales to the public (Federal Food and Drug Administration 1981).

The decline in the use of plant-based medicines after the early 1900s can be traced by changes in the United States Pharmacopeia (U.S.P.), the official U.S. guide to prescription and non-prescription drugs (United States Pharmacopeia (U.S.P.) 2004) (Figure 3). In 1916, 40 percent of the official medicinal preparations were crude plant extracts (United States Pharmacopeia (U.S.P.) 1916). The percentage of plants extracts listed in the Pharmacopeia, however, steadily declined after 1916, reaching 9 % in 1950 and 1 % by 1990 (United States Pharmacopeia (U.S.P.) 1950; 1990). While part of the decline in medicinal plant extracts recorded in the Pharmacopeia can be explained by an increase in the number of refined or synthetic drugs, the data actually indicate a significant reduction in the number of included plant extracts, decreasing from approximately 299 preparations in the 1916

Pharmacopeia to 60 and 49 preparations, respectively, in the 1950 and 1990

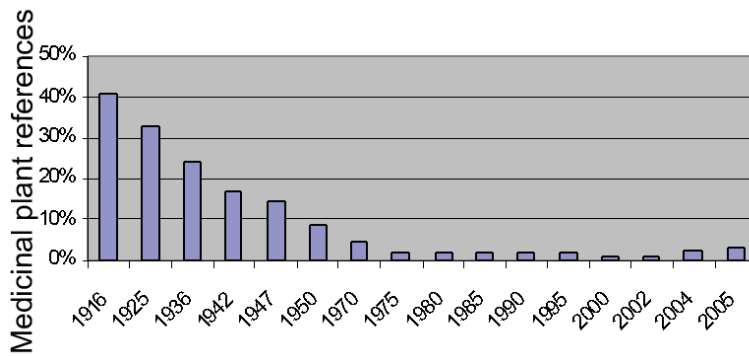


Figure 3. References to medicinal plants and extracts in U.S. Pharmacopeia

Pharmacopeias. Herbal remedies, such as St. Johns wort (*Hypericum perforatum*), echinacea (*Echinacea* spp.) and saw palmetto (*Serenoa repens*), which became popular in the late 1990s, were added to the Pharmacopeia in 2004 (United States Pharmacopeia (U.S.P.) 2004).

In the 1960s and 1970s, social and political forces gave rise to the hippies, a subculture of people disinterested in the workings of mainstream culture and ready to create self-sufficient communities of their own. This hippie subculture sought health and wellbeing by emphasizing the natural, focusing on diets with whole grains and vegetables and learning to treat basic ailments with medicinal plants. Others that tried this food and medicine regime discovered a healthier, more appealing lifestyle that years later became endorsed by dieticians and medical authorities (Alliance 2005). Such changes in lifestyle are evidenced by an increasing number of Americans choosing organically produced foods for their families (Table 2).

Table 2. U.S. organic-food sales

Year	Change
2002	+18.8 %
2003	+16.8 %
2004	+22.2 %

¹ Retail sales of organic foods and beverages reached \$10.4 billion in 2004; sales have been increasing at about 20 % annually since 1997

Thus, beginning in the 1980s, the American concept of medicine began to broaden from the conventional medical doctor prescribing a pill to cure an illness to include alternative medical systems that promoted a healthy lifestyle and the use of medicinal plants for prevention and treatment of illnesses. This shift from

conventional to alternative medicine in America has most likely been hastened by the expense of medical treatment (ASHP 1999) (Figures 4 and 5), the perceived arrogance of medical doctors (Duff 2002), the concern about side effects (ASHP 1999), the need for prescriptions (Alliance 2005) and the lack of cures for serious medical problems (such as cancer, cardiovascular disease and HIV infections) associated with conventional treatment. The change in the American medicinal system has been supported by changes in international views and immigration laws that brought alternative medicines to the forefront, including the opening of China that brought insights into acupuncture and the traditional Chinese medicine system

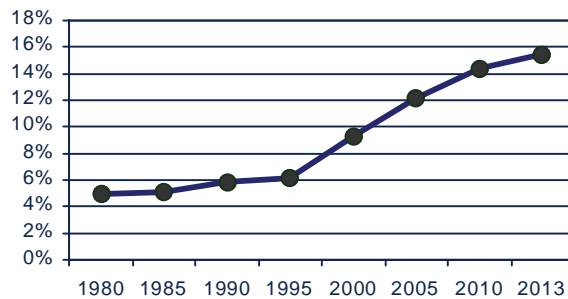


Figure 4. Pharmaceutical costs as percent of health care (data: BCBS 2005)

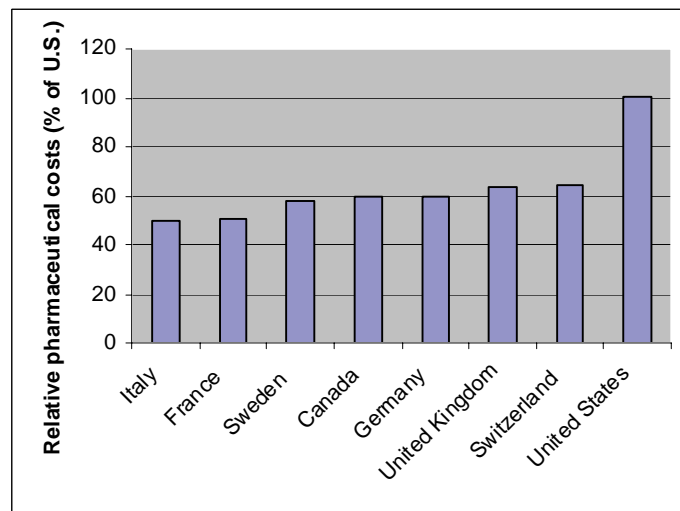


Figure 5. Relative pharmaceutical costs (data modified from Patented Medicine Prices Review Board 2003)

and the increased movement of Asians and Hispanics (many of whom have utilized traditional health systems) to America. In addition, the concern of an aging

American population – currently about 35 million Americans are over 65 (U.S. Census Bureau 2005) – about healthcare costs continued to push the elderly towards less expensive dietary supplements with fewer side effects than pharmaceuticals offered by conventional medicines (Adams 2004; Burstyn 2003).

The utilization of herbal products in the U.S. changed greatly with the passage of the Dietary Supplement Health and Education Act (DSHEA) in 1994 (U.S. Congress 1994). The passage of this law established medicinal botanicals as dietary supplements, an adjustment that categorized herbal medicinal products as foods, thus limiting the power of the FDA to restrict sales. This change in categorization developed because many products used as herbal medicines, such as garlic (*Allium sativum*) and ginger (*Zingiber officinale*), are also common food ingredients and could be purchased as foods, but not as medicines. The FDA retained control of product labelling and in this manner can assure that any health claims for a dietary supplement are limited (CDSL 1997). Enactment of DSHEA, however, helped consumers better understand and accept herbal medicines, spurring sales of herbal supplements (Figure 6).

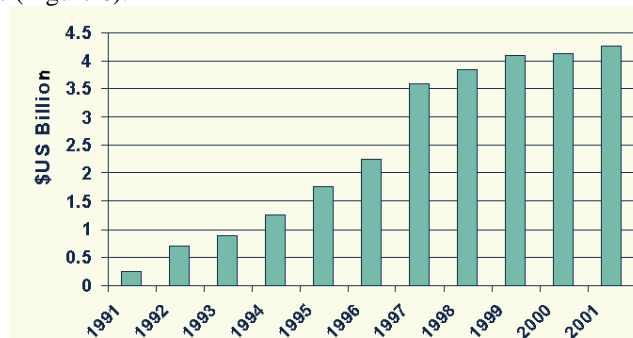


Figure 6. Sales of dietary supplements. Sales of over \$6 billion in U.S. are predicted by 2009 (Market Looks 2004)

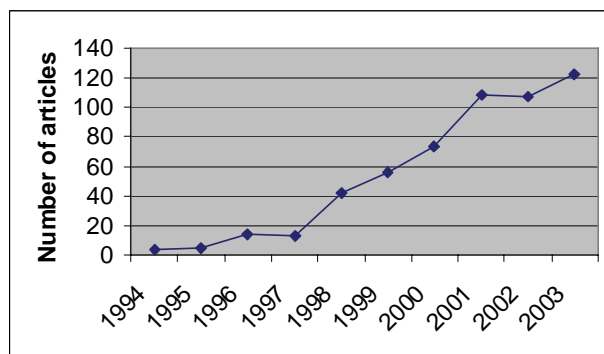


Figure 7. Published articles related to St. John's wort (data collected from Medline database 1994-2004)

Public interest and the need for a scientific information on herbal medicines has promoted research on popular supplements, as demonstrated by a search of the Medline medical database, which listed three published articles on St. John's wort (*Hypericum perforatum*) in 1994 and 123 published articles in 2003 (Figure 7).

After the passage of DHSEA and through 1998, herbal supplements received significant, mostly favourable, press coverage from mainstream media channels, publicity that stimulated sales of medicinal herbs and herbal products (Brevoort 1998). The favourable press coverage on medicinal plants, however, was short-lived, ending in 1999, as the media began publishing negative stories that cast medicinal herbs as either dangerous or ineffective and citing concerns about safety and efficacy (Figure 8). Negative stories from tests on efficacy have been highlighted to demonstrate herbal medicines were worthless, even though the studies were



"Thus, countless consumers are wasting their money on useless products or jeopardizing their health on hazardous ones."
(Brody 1999b)



"... not possible to say whether the herbal doses tested represented an amount that may actually reach the eggs or sperm" "... dietary supplements are not required to undergo premarket tests for safety or accuracy of dosage." (Brody 1999a)

Figure 8. Some press comments about botanical medicines in 1999

frequently poorly designed, tested herbal products on afflictions that were not traditionally treated with herbs, or used inaccurate *in vitro* models (ABC 2002; Davidson et al. 2002; Ondrizek et al. 1999). As a result of such negative press, sales of medicinal herbs slowed and decreased in 1999, and remained depressed through 2004.

The differences between medicinal plants and pharmaceutical drugs are important when considering the acceptance and use of these two products by the American public and the pharmaceutical industry. Much of the American public remains unsure about the safety and efficacy of medicinal plants and confused by the frequently extended time period for noticeable activity (as opposed to immediate responses usually attributable to conventional pharmaceuticals). In addition, consumers and medical professionals are often unaware of alternatives to conventional pharmaceuticals (bioactive, medicinal products, most with a single compound as the active ingredient), as national advertisements aimed at the public and medical personnel are relatively limited for dietary supplements, while conventional pharmaceuticals are generously promoted (\$3 billion spent on promotion in 2003) (Abramson 2004; Grassi 2004; Liebman 1997).

The safety of medicinal botanicals, frequently dismissed by advocates with the phrase "if it is natural, it must be good", is a justifiable, public concern. Opponents in the use of medicinal botanicals charge that to protect the health and safety of the public, dietary supplements should be required to undergo the same safety tests as conventional drugs before release to consumers. Yet, the value of such testing for public health is sometimes questionable, since FDA-approved conventional prescription drugs are reported to cause over 100,000 deaths and 1.5 million hospital admissions each year (Moore et al. 1998). In contrast, dietary supplements, not tested for safety by the FDA, cause only 5 - 30 deaths each year (Moore 2005). Botanically based dietary supplements can cause harm due to intrinsic chemical constituents, misidentification, contamination, contraindications and other similar problems, requiring the health-care practitioner and consumer to be knowledgeable about the benefits and potentially harmful effects of medicinal plants.

The government-lobbying potential of conventional pharmaceutical companies is well-funded as compared with dietary supplement companies, enabling the conventional pharmaceutical company, in contrast to the dietary-supplement producer, to have unsurpassed access to Congress and government regulators (Weisbrot 2002). Such lobbying efforts, directed at protecting market share of conventional pharmaceutical companies, are obviously effective or large sums of money would not be aimed at this effort. Conventional pharmaceuticals can be protected from competition by patents and, thus, become attractive investments for research, manufacturing and marketing. This patentability of conventional drugs contrasts with medicinal plant products that contain numerous, naturally occurring bioactive constituents and cannot be patented. While many manufacturers produce medicinal plant products for sale as dietary supplements, few are willing to support research and advertising (to physicians or possible patients) because consumers can easily purchase competitive brands.

Medicinal plants in America continue to be linked to consumers by a mixture of myth, tradition and science, thought by some to have magical power, used by some

following family recipes, and not trusted by some without definitive, scientific proof of efficacy (Craker 2003). Few Americans recognize the history of medicinal-plant use in the U.S. or appreciate that approximately 25 % of modern medicines were derived from or patterned after compounds in plants (Duke 1993; Farnsworth and Bingel 1977). Some current pharmaceutical companies began as distributors of medicinal plant products (Table 3).

Continued acceptance of medicinal plants for health care in America will undoubtedly depend on the professionalization of alternative health-care providers and continued research on the safety and efficacy of medicinal plants. Currently, naturopathic doctors (medical doctors trained with a focus on holistic health and natural remedies) are licensed to practice in 15 of the 50 states (AANMC 2005). Acupuncturists, some of whom prescribe Chinese herbal formulas, are licensed to practice in most states (AOM Alliance 2005). Herbalists, educated through trade schools or traditional apprenticeship programs, are not licensed to practice in any state, although efforts have been made by herbalists' organizations to professionalize the practice of medical herbalism through certification in a peer-reviewed process (AHG 2005). Any governmental recognition of this certification process, however, remains in the distant future.

Table 3. *Pharmaceuticals of Wyeth*

1881 ¹		2005 ²	
Aconite	Gentian	Alesse	Premphase
Aloes	Henbane	Altace	Prempro
Belladonna	Jalap	BeneFix	Prevnar
Black haw	Lobelia	Cordarone	Protonix
Buchu	Mandrake	Effexor	Rapamune
Calabar bean	Nux vomica	Enbrel	ReFacto
Cascara	Opium	HibTITER	Zosyn
Coca	Rhatany	Mylotarg	
Colocynth	Rhubarb	Neumega	
Digitalis	Senna	Phenergan	
Ergot	Serpentaria	Premarin	

¹ As recorded in an advertisement folio of the American Journal of Pharmacy, Vol. 53, 1881

² Featured Wyeth products for 2005, as listed at Wyeth website (www.wyeth.com)

Informal surveys of consumers at local markets in Massachusetts have suggested that in shopping for herbal supplements, consumers are concerned about product quality, safety, efficacy and wholesomeness. These consumer concerns are justified as third-party testing of herbal products indicates significant variation in constituents and constituent level among the same type of product (ConsumerLab 2004). While several manufacturers offer products standardized to the supposedly bioactive ingredient, the bioactive constituents and synergistic actions among constituents in medicinal plant material are not yet fully understood, making the determination of appropriate standards challenging.

The future direction and pharmaceutical use of medicinal plants in the U.S. remains difficult to predict. While many pharmacies and other shops in the U.S. provide a selection of herbal products, most lack staff with professional knowledge and experience about the use of these supplements. Only a few integrated pharmacies with stocks of conventional non-prescription and prescription medications and a variety of herbal, homeopathic and other natural health-care products have opened with supportive staff members trained in alternative therapies and able to answer questions from customers (McGregor 2004). Recent editorials and articles in U.S. medical journals suggest some acceptance of medicinal plants by medical doctors (Bent and Ko 2004). This acceptance may continue and grow if well-planned, clinical trials support the use of medicinal plants in therapy and issues of safety and standardization can be solved. Based on current trends of prescription-drug costs and consumer desires for natural health-care products in America, future American pharmacies may well offer product selection and educated staff supportive of conventional and alternative medicine systems, enabling the consumer and the medical practitioner to choose the best medicine, conventional or herbal, for maintaining health and for treatment of a medical condition.

REFERENCES

- AANMC, 2005. *Naturopathic medicine*. Association of Accredited Naturopathic Medical Colleges. Available: [http://www.aanmc.org/nat_med/] (23 Mar 2006).
- ABC, 2002. *St. John's wort study misinterpreted says herbal science group*. American Botanical Council, HerbalGram.org. Available: [<http://www.herbalgram.org/default.asp?c=040902press>] (23 Mar 2006).
- Abramson, J., 2004. *Overdo\$ed America: the broken promise of American medicine*. HarpersCollins Publishers, New York.
- Achilladelis, B., 1999. Innovation in the pharmaceutical industry. In: Landau, R., Achilladelis, B. and Scriabine, A. eds. *Pharmaceutical innovation: revolutionizing human health*. Chemical Heritage Press, Philadelphia, 1-147.
- Adams, M., 2004. *Elderly patients regularly prescribed dangerous medications with severe side effects*. NewsTarget.org (August 19). Available: [<http://www.newstarget.com/002032.html>] (23 Mar 2006).
- AHG, 2005. *AHG membership and AHG professional membership*. American Herbalist Guild. Available: [<https://www.americanherbalistsguild.com>] (23 Mar 2006).
- Alliance, 2005. *Compliance*. Alliance Healthcare Information. Available: [<http://www.alliancemsg.com/compliance.htm>] (23 Mar 2006).
- AOM Alliance, 2005. *Find a practitioner: looking for an acupuncturist or oriental medicine practitioner?* AOM Alliance. Available: [<http://www.aomalliance.org/>] (23 Mar 2006).
- ASHP, 1999. *ASHP patient concerns national survey research report*. American Society of Health-System Pharmacists. Available: [<http://www.ashp.org/pr/survey.cfm>] (23 Mar 2006).
- BCBS, 2005. *Medical cost reference guide: facts and trends to support knowledge-driven solutions*. Blue Cross Blue Shield Association. Available: [<http://www.bcbs.com/mcrg/>] (23 Mar 2006).
- Bent, S. and Ko, R., 2004. Commonly used herbal medicines in the United States: a review. *American Journal of Medicine*, 116 (7), 478-485.
- Blumenthal, M., 2005. Herb sales down 7.4 percent in mainstream market. *HerbalGram*, 66, 63. [<http://herbalgram.org/naturemade/herbalgram/articleview.asp?a=2828>]
- Brevoort, P., 1998. The booming U.S. botanical market: a new overview. *HerbalGram*, 44, 33-46. [<http://herbalgram.org/naturemade/herbalgram/articleview.asp?a=1309>]
- Brody, J.E., 1999a. Herbal remedies tied to pregnancy risks. *New York Times* (March 9). [<http://www.nytimes.com/>]
- Brody, J.E., 1999b. Americans gamble on herbs as medicine. *New York Times* (February 9). [<http://www.nytimes.com/>]

- Buffum, H.E., Lovering, A.T., Warren, I., et al., 1905. *The household physician: a twentieth century medic*. Woodruff Publishing, Boston.
- Burstyn, B.S., 2003. Conventional medicine: far riskier than supplements. *New Zealand Herald* (June 16 2003).
[http://www.newmediaexplorer.org/sepp/2003/06/16/conventional_medicine_far_riskier_than_supplements.htm]
- CDSL, 1997. *The report of the Commission on Dietary Supplement Labels*. Commission on Dietary Supplement Labels. [<http://www.health.gov/dietsupp/final.pdf>]
- CERHR, 2002. *Thalidomide*. The National Toxicology Program, Center for the Evaluation of Risks to Human Reproduction. Available: [<http://cerhr.niehs.nih.gov/common/thalidomide.html>] (23 Mar 2005).
- ConsumerLab, 2004. *Many Echinacea supplements don't meet quality standards according to ConsumerLab.com: test results of cold-reducing herbal supplements released*. ConsumerLab.com. Available: [http://www.consumerlab.com/news/news_031804.asp] (24 Mar 2006).
- Corish, J.L., 1938. *Health knowledge: a thorough and concise knowledge of the prevention, causes, and treatments of disease, simplified for home use*. Medical Book Distributors, New York.
- Craker, L.E., 2003. Production and demand: a view to the future of MAP. In: Bernáth, J. and Szoke, E. eds. *Proceedings of the international conference on medicinal and aromatic plants: part II (follow up of Acta horticultrae 576), Budapest, Hungary, 8-11 July, 2001*. ISHS, Leuven, 15-27. Acta Horticulturae no. 597.
- Davidson, J.R.T., Gadde, K.M., Fairbank, J.A., et al., 2002. Effect of *Hypericum perforatum* (St John's wort) in major depressive disorder: a randomized controlled trial. *JAMA - Journal of the American Medical Association*, 287 (14), 1807-1814.
- Duff, P., 2002. Professionalism in medicine: an A-Z primer. *Obstetrics and Gynecology*, 99 (6), 1127-1128.
- Duke, J.A., 1993. Medicinal plants and the pharmaceutical industry. In: Janick, J. and Simon, J.E. eds. *New crops: proceedings of the second national symposium New crops; exploration, research, commercialization*. Wiley, New York, 664-669. [<http://www.hort.purdue.edu/newcrop/proceedings1993/V2-664.html>]
- Farnsworth, N.R. and Bingel, A.S., 1977. Problems and prospects of discovering new drugs from higher plants by pharmacological screening. In: Wagner, H. and Wolff, P. eds. *New natural products and plant drugs with pharmacological, biological or therapeutical activity*. Springer, Berlin, 1-22.
- Federal Food and Drug Administration, 1981. The story of the laws behind the labels. *FDA Consumer*, 16 (3). [<http://www.cfsan.fda.gov/~lrd/history1.html>]
- Flexner, A., 1910. *Medical education in the United States and Canada: a report to the Carnegie Foundation for the Advancement of Teaching*. Carnegie Foundation, New York. Carnegie Bulletin no. 4.
- Grassi, D.M., 2004. *Spending by U.S. drug manufacturers reaps rewards*. Elites TV. Available: [<http://www.elitestv.com/pub/2005/Jul/EEN42d473f58c2fe.html>] (24 Mar 2006).
- Griggs, B., 1981. *The green pharmacy: the history and evolution of western herbal medicine*. Healing Arts Press, Manchester.
- Hoffman, B.G., 1964. John Clayton's 1687 account of the medicinal practices of the Virginia Indians. *Ethnohistory*, 11 (1), 1-40. [<http://links.jstor.org/sici?sici=0014-1801%28196424%2911%3A1%3C1%3AJC1AOT%3E2.0.CO%3B2-0>]
- Jayne, D., 1883. *Dr. Jayne's medical almanac*. Dr. D. Jayne & Sons, Philadelphia.
- Kavasch, E.B. and Baar, K., 1999. *American Indian healing arts: herbs, rituals, and remedies for every season of life*. Bantam Books, New York.
- Liebman, M., 1997. Hard facts about a soft spend: how print advertising pays off. *Medical Marketing and Media*, 32 (4), 66-74. [http://www.amponline.org/MJA/Soft_Spend.html]
- Lloyd, J.U., 1911. *History of vegetable drugs of the Pharmacopeia of the United States*. Lloyd Library, Cincinnati. Pharmacy Series no. 4. [http://www.swsbm.com/ManualsOther/USP_Drug_History_Lloyd.pdf]
- Lloyd, J.U. and Lloyd, C.G., 1884-1887. *Drugs and medicines of North America: a collection of publications written by the Lloyd brothers and others. See, for example, bulletins in Reproduction Series no. 1-6*. Lloyd Library. Available: [<http://www.henriettesherbal.com/eclectic/dmna/index.html>] (24 Mar 2006).

- Market Looks, 2004. *MarketLooks: nutritional supplements*. MarketLooks, Packaged Facts. Available: [<http://academic.marketresearch.com/>] (Feb 2005).
- McGregor, H.E., 2004. Squeeze in a yoga class while you wait for your prescription; 'Natural' pharmacies offer herbalist, naturopaths, and more to a public eager for alternative therapies. *Los Angeles Times* (Dec 10, section health, part F). [http://www.greatspiritventures.com/pdfs/article_1.pdf]
- Moore, T.J., 2005. *Supplements: dangerous herbal products*. Thomas J. Moore website. Available: [http://www.thomasjmoore.com/pages/dietary_part7.html] (24 Mar 2006).
- Moore, T.J., Psaty, B.M. and Furberg, C.D., 1998. Time to act on drug safety. *JAMA - Journal of the American Medical Association*, 279 (19), 1571-1573.
- National Academy of Science, 2004. *Science, medicine, and animals*. National Academies Press, Washington. [<http://darwin.nap.edu/books/0309088941/html/>]
- Ondrizek, R.R., Chan, P.J., Patton, W.C., et al., 1999. An alternative medicine study of herbal effects on the penetration of zone-free hamster oocytes and the integrity of sperm deoxyribonucleic acid. *Fertility and Sterility*, 71 (3), 517-522.
- Patented Medicine Prices Review Board, 2003. *PmPrB annual report 03*. Available: [<http://www.pmprb-cepmb.gc.ca/CMFiles/ar2003e30LWY-1062004-5966.pdf>].
- Remington, J.P. and Wood, H.C. (eds.), 1918. *The dispensatory of the United States of America*. 20th edn. Lippincott, Philadelphia. [<http://www.swsbm.com/Dispensatory/USD-1918-complete.pdf>]
- Richardson, J.G., Ford, W.H. and Vanderbeck, C.C., 1905. *Medicology or home encyclopedia of health: a complete family guide*. University Medical Society, New York.
- U.S. Census Bureau, 2005. *U.S. Census 2000: state and county quick facts: quick, easy access to facts about people, business, and geography*. Available: [<http://quickfacts.census.gov/qfd/>] (24 Mar 2006).
- U.S. Congress, 1994. *The dietary supplement health and education act of 1994: public law 103-417; 103rd Congress of the United States of America*. Available: [<http://www.fda.gov/opacom/laws/dshea.html>] (24 Mar 2006).
- United States Pharmacopeia (U.S.P.), 1916. *The pharmacopeia of the United States of America*. 9th edn. Charles Ewer, Boston.
- United States Pharmacopeia (U.S.P.), 1950. *The pharmacopeia of the United States of America*. 14th edn. Charles Ewer, Boston.
- United States Pharmacopeia (U.S.P.), 1990. *The pharmacopeia of the United States of America*. 22nd edn. Charles Ewer, Boston.
- United States Pharmacopeia (U.S.P.), 2004. *The pharmacopeia of the United States of America*. 27th edn. United States Pharmacopeial Convention, Rockville.
- Weisbrot, M., 2002. *The cost of protectionism in pharmaceuticals*. Center for Economic Policy and Research. Available: [http://www.cepr.net/columns/weisbrot/cost_of_protectionism.htm] (24 Mar 2006).
- Weishan, M., 1999. *The new traditional garden: a practical guide to creating and restoring authentic American gardens for homes of all ages*. Ballantine Publishing Group, New York.