Herbal Medicines in Pregnancy & Lactation

An Evidence-Based Approach

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CONTENTS

PREFACE

Exposures to over-the-counter products are frequent in pregnant women. Perhaps this is a paradoxical response to the decreased use of prescribed medications during pregnancy for fear of teratogenicity. For many women, natural health products such as herbal medicines or supplements may seem a reasonable alternative as the lay media often portrays natural medicines as safe. While the true incidence of natural product use in pregnancy is not known, some studies suggest that as high as sixty percent of pregnant women use natural therapies including herbal medicines either during pregnancy or while planning.[1] Pregnant women often consider the use of natural products such as peppermint tea or ginger to help with symptoms of pregnancy such as nausea and vomiting.[2] In one study of midwives practicing in North Carolina, half of the respondents admitted to recommending herbal medicines to their patients for pregnancy related conditions.[3] Further to this intended use, it must be remembered that nearly half of all pregnancies are unplanned and unexpected exposures to medicines and supplements in the first trimester are not rare.

Despite the prevalent use of natural health products by pregnant women, there is very little published evidence with regards to the safety and efficacy of natural health products during pregnancy and lactation. Many modern and classic texts warn against the use of natural product supplementation during pregnancy or lactation for up to one-third of the products listed in their monographs. However, most resources provide little information on the data used to evaluate reproductive toxicity apart from reports of historical use of herbs as abortifacients or uterine stimulants or animal data of genotoxicity or teratogenicity. Data on efficacy during pregnancy is similarly scarce from most texts.

To our knowledge, ours is the first text that aims to specifically address the lack of data of natural health product use in pregnancy and lactation. While it is not an exhaustive compendium of available supplements, it is a comprehensive listing of common herbs, vitamins and supplements used by pregnant women. Drawing on all available studies obtained through meta-analytic techniques, we have graded the quality of evidence on natural product safety during pregnancy and breastfeeding. Statements in traditional texts such as 'use of this herbal product should occur only after careful assessment of the benefits and risks' need clarification with up-to-date evidence from the medical literature. Busy healthcare providers need to have access to quick and reliable information they can use to help address patient concerns with regards to natural health product use in pregnancy or lactation. We hope that this text will be received as a valuable resource for all clinicians who treat pregnant patients. As natural

health supplements continue to gain popularity, we anticipate that the utility for a text such as this will grow too.

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References

1. Maats FH, Crowther CA. Patterns of vitamin, mineral, and herbal supplementation use prior to and during pregnancy. Aust NZ J Obstet Gynaecol 2002; 42:494–496.
2. Hollyer T, Boon H, Georgousis A, Smith M, Einarson A. The use of CAM by women suffering from nausea and vomiting during pregnancy. BMC Complementary and Alternative Medicine 2002; 2:5
3. Allaire AD, Moss M-K, Wells SR. Complementary and alternative medicine in pregnancy: a survey of North Carolina certified nurse-midmives. Obstet Gynecol 2000; 95:19–23.

Chapter 1

TRADITIONAL BOTANICAL MEDICINES

Paul Richard Saunders

Introduction

Pregnancy and subsequent lactation have been an essential part of human existence for millennia, but unfortunately the experience has not been easy for all women. Some of our earliest medicines were plants used to address the difficulties and complications of these biologic processes and to better prepare the expectant mother for pregnancy, delivery, and lactation. In many part of the world women still use herbal medicines even when attended by Western medicine.[1,2] This short review from an historical perspective will first examine some of the botanicals that have been used during pregnancy and delivery and then during lactation. Reference will also be made to some of the scientific literature on these botanical medicines.

Contraception and pregnancy

Although conception is a problem for some women, a more common problem is contraception. In rural Mindanao (the Philippines) women still drink kamias and other herbal preparations rather than use oral contraceptives.[2] Quisumbing's thorough study of Philippine medicinal plants identified over 60 plants used as abortifacients and over 130 plants used as emmenagogues.[3] Of interest is *Kibatalia blancoi* and *K. gitingesis* whose leaf and bark may have progesterone-like effects.[4,5] A 1995–1996 reproductive health survey of 6465 Paraguayan women of reproductive age found they were most familiar (88%) with yuyos, a variety of herbs usually drunk as a tea daily to prevent pregnancy.[6] Studies in India to find traditional, effective contraceptives have focused on *Hibiscus rosa-sinensis*, Rudrapushpaka, *Embelia ribes*, *Daucus carota*, *Butea monosperma*, *Sapindus trifoliatus*, *Mentha arvensis*, *Ferula jaeschkeana*, and several others because of their anti-implantation activity.[7] Herbs with potential as a male contraceptive are *Gossypium herbaceum* and *Tripterygium wilfordii*.[7]

In traditional Chinese medicine, a core of 10–20 herbs is used in pregnancy.[8] A review of traditional Chinese materia medica would, based on clinical tongue and pulse diagnosis, include plants used for liver cleansing, blood regulating, qi tonics, yin tonics and warming.[9] *Striga asiatica* is one herb being studied as a contraceptive.[10]

Moerman has published an exhaustive description of the plants used by native North Americans; abortifacients number over 100 and female gynecological aids nearly 350.[11] A large number of these plants came to the knowledge of European settlers by inquiry and observation with subsequent clinical use in patients. When the outcome was repeatedly successful this was recorded and the details of its use refined from repeated use by Eclectic physicians who

differentiated between more effective and less well studied botanical medicines in *King's American Dispensatory*.[12]

Vitex agnus-castus has over a 2000-year history in female menstrual regulation including infertility. It has also been shown to have beneficial effects for lactation, making it in a sense a botanical alpha and omega of pregnancy and lactation.[13–15] Once the woman was pregnant *Rubus idaeus* leaf was used by the Cherokee for labor pains and by the Cree and Cherokee to slow uterine bleeding; benefits were attributed to its astringent and tannin properties.[16,17] It is a well-known partus preparator or parturient taken during pregnancy to tonify the uterus, maintain pregnancy and ease delivery.[18,19]

One complication of pregnancy is threatened miscarriage. A well-known herbal formula that prevents this is *Viburnum prunifolium*, *Leonurus cardiaca*, and *Mitchella repens*.[20] *Viburnum prunifolium* was used by the Delaware and Micmac to strengthen and tone the uterus during pregnancy, and by the Eclectics to calm uterine colic, for threatened miscarriage and painful uterine contractions.[21,22] *L. cardiaca* was regarded as a sedative for female nervousness and hysteria, and for general female complaints by the Cherokee, Delaware, Iroquois, Micmac, Mohegan, and Shinnecock as well as by the Eclectics.[23,24] *M. repens* was used by the Cherokee, Delaware, Iroquois and Menominee for a variety of complaints regarding the uterus.[25] The Eclectics considered it one of the most important herbs for successful pregnancy, to prevent miscarriage, throughout the pregnancy for complications, and in the last weeks to ease delivery.[26,27] This botanical formula was designed to address the uterine problems, anxiety, nervousness, and pain that could accompany a possible miscarriage.

As the pregnancy neared completion a partus preparator was often given to the expectant woman in the last 3–6 weeks to prepare the uterus for delivery and reduce the pain of delivery. Botanicals drawn upon to affect the uterine circulation and musculature included *M. repens*, *V. prunifolium*, *Caulophyllum thalictroides*, *Actea* (*Cimicifuga*) *racemosa*, *Aralia nudicaulis*, and for nervines included those such as *Leonurus cardiaca*, *Nepeta cataria*, and *Gelsemium sempervirens*.[26,28,29] The dose of *C. thalictroides* was minimal before and during labor to avoid fetal distress.[29,30] Its Native American use related to pregnancy and labor included the Cherokee, Menominee, Ojibwa, and Potawatomi.[31] *G. sempervirens* was used to calm the patient and help dilate the os in stalled labor.[32,33]

The preferred botanical to address post-labor pains was *G. sempervirens*.[32,33] Dose and timing were critical as administration too early or too frequent could slow the labor process and too much after labor could make the woman too drowsy to look after her newborn infant.[32]

Hemorrhage was the first severe complication after delivery as it could not only cause considerable blood loss and profound anemia, but also lead to death if unchecked. *Cinnamomum zeylanicum* was a preferred antihemorrhagic.[28,34,35] It also provided some anti-microbial protection from puerperal fever, a important complication arising from infection contracted during or after labor that took the life of many new mothers. *C. zeylanicum* is still used

in traditional Chinese medicine for this type of fever.[36] Other anti-hemorrhagics included *Capsella bursa-pastoris* and *Geranium maculatum* whereas botanicals preferred for post-partum anti-fever were *Veratrum viride* and *Atropa belladonna*.[37]

In traditional Chinese medicine *Angelica sinensis* supplements blood, tones the uterus and is often used throughout the pregnancy. Its stimulating or inhibiting effect on the uterus is regulated by how long it is decocted in a larger formula.[38] In contrast, Western pharmacologists label it an abortifacient and strongly recommend against its use in pregnancy.[39] *Rehmannia glutinosa* is a nutritive tonic that nourishes yin and blood and can be of benefit in bleeding, *Paeonia lactiflora* can disperse blood thus controlling pain, and *Cyperus rotundus* can control bleeding as well as antepartum and post-partum headache pain.[40] Three additional traditional Chinese medicinal herbs of note are *Fritillaria cirrhosa* for regulating uterine contractions and blood loss after labor, *Poncirus trifoliata* to relieve pain and regulate uterine contractions, and *Codonopsis pilosula* to build qi, address weakness, fatigue, and loss of appetite – symptoms often present in the first trimester, near the end of pregnancy, or after delivery.[41]

An indirect use of traditional Chinese medicinal herbs is moxibustion (charcoal from *Artemisia argyi* and related species).[42] In a randomized human study it increased fetal activity during treatment and cephalic presentation after treatment and at delivery.[43] A study of recurrent spontaneous abortion using the traditional Chinese medicinal formula zhibai dihuang, with herbs to remove evil heat, dampness, replenish blood and activate circulation, altered anti-ABO group antibodies and yielded a high number of normal deliveries.[44]

Lactation

Mother's breast milk is still regarded as best and in some settings is the infant's only chance for survival. A study of new mothers attending breast-feeding clinics in Canada found up to 15% reported insufficient milk supply.[45] No doubt this has been a problem in some women, leading to efforts to identify herbal remedies across a diversity of cultures. Brückner has reviewed the herbal drugs most commonly used in Europe.[46] Bingel and Farnsworth have produced the most thorough review to date, identifying over 400 plants that have been used ethnomedically and recorded in the literature as galactagogues.[47] Not even 10% of the plants have been studied scientifically so their individual mechanism and effectiveness as galactagogues is generally unknown.

Breast pain, swelling, hardness, and even mastitis have been treated with *Phytolacca americana*, *Ricinus communis*, and *M. repens,* all of which can be applied topically before or between breast feeding. They must be cleansed from the breast prior to nursing.[48] A possible mechanism is their ability to facilitate flow from the gland through the nipple and to the infant.[47]

In Central America, Mayan and other native women use a variety of herbs to increase breast milk production. *Coffea arabica* and *Camellia sinensis* are two diuretics that contain caffeine, and caffeine and theophylline, respectively, and

have been used – and shown experimentally – to promote lactation.[47] Caffeine in some infants can lead to insomnia and colic. *Euphorbia lancifolia* has been used by humans for centuries and may also increase milk production in cows.[49]

Emotions such as fear and anxiety may reduce the release of milk suggesting a role for herbs that reduce the psychological and physiological effects of emotions.[47] *Lactuca virosa* and *L. sativa* produce a dried sap used for sedation, whereas *L. biennis* has been used to ease breast pain and promote lactation.[50,51] *Anethum graveolens* is a sedative that has been used with some benefit.[47,52] Sedative plants often contain essential oils, compounds that dilate blood vessels, relax muscles, and enhance sleep. Noteworthy are *Origanum vulgare* employed in fomentations, *Lavandula officinal*, *L. angustifolia*, and *L. vera* that are added to baths or applied locally for pain, and *Mentha piperita*, *M. viridis*, and *Nepeta cataria* taken as an infusion.[53]

Beer, a well-known galactagogue, contains *Humulus lupulus*, noted for both its sedative action and estrogenic effect on breast tissue, and *Hordeum vulgare*, reputed to be galactogenic and to cause prolactin release.[47,54] *H. lupulus* can be applied to painful swellings such as of the breast, but is generally empirically contraindicated in depression.[55,56]

Other galactagogues of note include *Urtica dioica* and *U. urens* which can be applied topically or taken internally.[57] *Galega officinalis* has enjoyed more popularity in its native Europe than North America for it ability to stimulate milk production.[58,59] *Trigonella foenum-graecum* has historically been widely used in Europe and North Africa and some of the animal data are positive.[60,61] *Salvia officinalis* is used more as a lactation regulator, most often to reduce milk production and pain when the baby has been weaned.[62,63]

Ayurveda, the traditional medicine of India, has yielded such galactagogues as *Rauwolfia serpentina*, *R. oreogiton*, and *R. volkensii*, whose use is supported by endocrinology and findings from clinical trials that have focused on its alkaloid content. Reserpine, a dopamine-depleting agent can produce galactorrhea in women and decrease anxiety, and several other alkaloids have similar activity.[47] There is positive data for *Leptadenia reticulata* as well.[47] *Asparagus racemosus* was examined in a clinical trial where it was used in a herbal formula with six other herbs, but the results were not significant.[64] Current and future research could increase our knowledge about other herbs used traditionally in rural India.[65]

Traditional Chinese medicinal botanicals for enhancing milk production in humans include *Astragalus membranaceus*, *Taraxacum mongolicum*, *Tetrapanax papyrifera*, *Liquidambar taiwaniana*, and *Ligusticum chuaniong* (*L. striatum*) to name a few.[66] In general these are qi, yin, and/or blood tonics.

Summary

The use of medicinal plants to address infertility, maintain pregnancy, ease the birthing process, and aid in milk production or its cessation has been identified in many cultures, several of whom have complex medical systems.[1,2,4,6,9,11,65,67] Over 400 plants have been identified as ethnomedically affecting lactation.

Unfortunately, modern science has not maintained pace in the study of the mechanisms and relative benefit or potential harm of these plants. Women from many cultural backgrounds continue to use plants despite the presence of modern medications. More detailed study in this area could yield new information about mammalian reproductive endocrinology and physiology, plant pharmacognosy and constituent physiology, and identify the larger potential of at least some of these plants.

References

1. Mabina MH, Moodley J, Pitsoe SB. The use of traditional herbal medication during pregnancy. Trop Doct 1997; 27:84–86.
2. Quijano N Jr. Herbal contraceptives: exploring indigenous methods of family planning. Initiatives Popul 1986; 8:22, 31–35.
3. Quisumbing E. Medicinal plants of the Philippines. Caloocan City, Philippines: Katha Publishing, 1978:1079, 1110–1111.
4. Guerrero AM. Age-old methods of contraception. Initiatives Popul 1977; 3:20–25.
5. Quisumbing E. Medicinal plants of the Philippines. Caloocan City, Philippines: Katha Publishing, 1978:729.
6. Bull SS, Melian M. Contraception and culture: the use of yuyos in Paraguay. Health Care Women Int 1998; 19:49–60.
7. Chaudhery RR. The quest for a herbal contraceptive. Natl Med J India 1993; 6:199–201.
8. Wong HB. Effects of herbs and drugs during pregnancy and lactation. J Singapore Paediatr Soc 1979; 21:169–178.
9. Hsu HY. Oriental materia medica: a concise guide. Long Beach, CA: Oriental Healing Arts Institute, 1986:6–18.
10. Chaing HS, Merino-Chavez G, Yang LL, Wang FN, Hafez ES. Medicinal plants: conception/contraception. Adv Contracept Deliv Syst 1994; 10:355–363.
11. Moerman DE. Native American ethnobotany. Portland, OR: Timber Press, 1998:765, 799–801.
12. Felter HW, Lloyd JU. King's American Dispensatory, 18th ed, 1905. Reprinted, Sandy, OR: Eclectic Medical Publications, 1983:iii–iv.
13. McCutcheon AR, Chastebarry IN, Chandler F, eds. Herbs everyday reference for health professionals. Ottawa, ON: Canadian Pharmacists Association, Canadian Medical Association, 2000:76–68.
14. Witman G, Gerhard I, Runnebaum B. The efficacy of the herbal drug Mastodynon in femal infertility. Arch Gynecol Obstet 1993; 254:158–160.
15. Du Mee C. Vitex agnus castus. Aust J Herbal Med 1993; 5:63–65.
16. Moerman DE. Native American ethnobotany. Portland, OR: Timber Press, 1998:488–489.
17. Felter HW, Lloyd JU. King's American Dispensatory, 18th ed, 1905. Reprinted. Sandy, OR: Eclectic Medical Publications, 1983:1680–1683.
18. Scientific Committee. British herbal pharmacopoeia. Bournemouth, UK: British Herbal Medicine Association, 1995:182.
19. Mitchell WA Jr. Plant medicine in practice using the teachings of John Bastyr. St. Louis, MO: Elsevier Science, 2003:266.
20. Harper-Shove F. Prescriber and Clinical Repertory of Medicinal Herbs. Rustington, Sussex, UK: Health Science Press, 1938:99.

21. Moerman DE. Native American Ethnobotany. Portland, OR: Timber Press, 1998:595.
22. Felter HW, Lloyd JU. King's American Dispensatory, 18th ed, 1905. Reprinted. Sandy, OR: Eclectic Medical Publications, 1983:2059–2062.
23. Moerman DE. Native American Ethnobotany. Portland, OR: Timber Press, 1998:301.
24. Felter HW, Lloyd JU. King's American Dispensatory, 18th ed, 1905. Reprinted. Sandy, OR: Eclectic Medical Publications, 1983:1125–1126.
25. Moerman DE. Native American Ethnobotany. Portland, OR: Timber Press, 1998:345–346.
26. Mitchell WA Jr. Plant medicine in practice using the teachings of John Bastyr. St. Louis, MO: Elsevier Science, 2003:386.
27. Felter HW, Lloyd JU. King's American Dispensatory, 18th ed, 1905. Reprinted. Sandy, OR: Eclectic Medical Publications, 1983:1273–1274.
28. Harper-Shove F. Prescriber and clinical repertory of medicinal herbs. Rustington, Sussex, UK: Health Science Press, 1938:103–104.
29. Felter HW, Lloyd JU. King's American Dispensatory, 18th ed, 1905. Reprinted. Sandy, OR: Eclectic Medical Publications, 1983:468–472, 528–553, 916–923.
30. Wilson C. Useful Prescriptions. Cincinnati, OH: Lloyd Brothers Pharmacists, 1935: 102.
31. Moerman DE. Native American Ethnobotany. Portland, OR: Timber Press, 1998:144.
32. Felter HW, Lloyd JU. King's American Dispensatory, 18th ed, 1905. Reprinted. Sandy, OR: Eclectic Medical Publications, 1983:916–923.
33. Wilson C. Useful Prescriptions. Cincinnati, OH: Lloyd Brothers Pharmacists, 1935: 108.
34. Wilson C. Useful Prescriptions. Cincinnati, OH: Lloyd Brothers Pharmacists, 1935: 103.
35. Felter HW, Lloyd JU. King's American Dispensatory, 18th ed, 1905. Reprinted. Sandy, OR: Eclectic Medical Publications, 1983:557–560.
36. Hsu HY. Oriental materia medica a concise guide. Long Beach, CA: Oriental Healing Arts Institute, 1986:375–376.
37. Felter HW, Lloyd JU. King's American Dispensatory, 18th ed, 1905. Reprinted. Sandy, OR: Eclectic Medical Publications, 1983:431–434, 927–929, 331–340, 2050–2054.
38. Hsu HY. Oriental materia medica a concise guide. Long Beach, CA: Oriental Healing Arts Institute, 1986:540–542.
39. Barnes J, Anderson LA, Phillipson JD. Herbal medicines, 2nd ed. London, UK: Pharmaceutical Press, 2002:47–50.
40. Hsu HY. Oriental materia medica a concise guide. Long Beach, CA: Oriental Healing Arts Institute, 1986:148–149, 415–416, 546, 548–549.
41. Hsu HY. Oriental materia medica a concise guide. Long Beach, CA: Oriental Healing Arts Institute, 1986:407–409, 526–527, 679–680.
42. Bensky D, Gamble A. Chinese herbal medicine: materia medica, 2nd ed. Seattle, WA: Eastland Press, 1993:259–260.
43. Cardini F, Weixin H. Moxibustion for the correction of breech presentation: a randomized controlled trial. JAMA 1998; 280:1580–1584.
44. Li DJ, Li CJ, Zhu Y. Treatment of integrated traditional and western medicine in recurrent spontaneous abortion of immune abnormality type [English Abstract]. Zhongguo Zhong Xi YiJie He Za Zhi 1997; 17:390–392.

45. MacIntosh HC. What is the pharmacological basis for the action of herbs that promote lactation and how can they best be utilized Part I. Can J Herbalism 2003; XXIV:15–19, 36.
46. Brückner C. Anwendung and wert in europa gebräuchlicher lactationsördernder heilpflanzen (galactagoga) [English Abstract]. Pädiatr Grenzgeb 1989; 28:403–410.
47. Bingel AS, Farnsworth NR. Higher plants as potential sources of galactagogues. In: Wagner H, Farnsworth NR, eds. Economic and medicinal plant research volume 6. London, UK: Academic Press, 1994:1–54.
48. Felter HW, Lloyd JU. King's American Dispensatory, 18th ed, 1905. Reprinted. Sandy, OR: Eclectic Medical Publications, 1983:1471–1475, 1380–1383, 1273–1274.
49. Rosengarten F Jr. A neglected Mayan galactagogue – ixbut (Euphorbia lancifolia). J Ethnopharmacol 1982; 5:91–112.
50. Felter HW, Lloyd JU. King's American Dispensatory, 18th ed, 1905. Reprinted. Sandy, OR: Eclectic Medical Publications, 1983:1114–1117.
51. Moerman DE. Native American Ethnobotany. Portland, OR: Timber Press, 1998:294.
52. Felter HW, Lloyd JU. King's American Dispensatory, 18th ed, 1905. Reprinted. Sandy, OR: Eclectic Medical Publications, 1983:203.
53. Felter HW, Lloyd JU. King's American Dispensatory, 18th ed, 1905. Reprinted. Sandy, OR: Eclectic Medical Publications, 1983:1420, 1123–1124, 1254–1256, 1252.
54. Felter HW, Lloyd JU. King's American Dispensatory, 18th ed, 1905. Reprinted. Sandy, OR: Eclectic Medical Publications, 1983:996–1000.
55. Felter HW, Lloyd JU. King's American Dispensatory, 18th ed, 1905. Reprinted. Sandy, OR: Eclectic Medical Publications, 1983:998–1000.
56. Brinker F. Herb Contraindications and Drug Interactions. Sandy, OR: Eclectic Medical Publications, 2001:119.
57. Felter HW, Lloyd JU. King's American Dispensatory, 18th ed, 1905. Reprinted. Sandy, OR: Eclectic Medical Publications, 1983:2032–2034.
58. Felter HW, Lloyd JU. King's American Dispensatory, 18th ed, 1905. Reprinted. Sandy, OR: Eclectic Medical Publications, 1983:908.
59. Weiss RF. Herbal Medicine, 6th ed. Beaconsfield, UK: Beaconsfield Publishers, 1988:318.
60. Weiss RF. Herbal Medicine, 6th ed. Beaconsfield, UK: Beaconsfield Publishers, 1988:199, 336.
61. MacIntosh HC. What is the pharmacological basis for the action of herbs that promote lactation and how can they best be utilized part II. Can J Herbalism 2003; XXV:15–11, 38.
62. Felter HW, Lloyd JU. King's American Dispensatory, 18th ed, 1905. Reprinted. Sandy, OR: Eclectic Medical Publications, 1983:1705–1706.
63. Weiss RF. Herbal medicine, 6th ed. Beaconsfield, UK: Beaconsfield Publishers, 1988:228.
64. Sharma S, Ramji S, Kumari S, Bapna JS. Randomized controlled trial of Asparagus racemosus (Shatavari) as a lactogogue in lactational inadequacy. Indian Pediatr 1996; 33:675–677.
65. Anon. Learning from India's traditional birth attendants, the dais. Arrows Change. 199; 5:3.

66. Hsu HY. Oriental Materia Medica a Concise Guide. Long Beach, CA: Oriental Healing Arts Institute, 1986:521–523, 237–238, 311–312, 465, 446–447.
67. Raden-Sanusi HR, Werner R. The role of traditional healers in the provision of health care and family planning services: Malay traditional and indigenous medicine. Malays J Reprod Health 1985; 3(Suppl 1):S82–S89.

Chapter 2

PHARMACOGNOSY – THE SCIENCE OF NATURAL SOURCE MEDICINES

The study of medicinal plants and their properties is called **pharmacognosy**. This science has led to the development of many drugs in use today including aspirin (the basic salicylate structure was discovered from the white willow while aspirin was synthesized from meadowsweet), opioids (originally from opium poppies), the birth control pill (synthesized from steroid structures found in a wild Mexican yam), and chemotherapeutic agents like vincristine and vinblastine (from Madagascar periwinkle) or taxol (from the Pacific yew tree).

Today, herbal medicine is big business. However, there is much confusion about what herbal medicine is and is not. While pharmacognosy is a science that deals with the discovery of medicines from natural substances, it is certainly not the same as herbalism. According to the American Society of Pharmacognosy, its scope includes 'the study of the physical, chemical, biochemical and biological properties of drugs, drug substances, or potential drugs or drug substances of natural origin as well as the search for new drugs from natural sources. Research problems in pharmacognosy include studies in the areas of phytochemistry, microbial chemistry, biosynthesis, biotransformation, chemotaxonomy, and other biological and chemical sciences'. The term **herbalism** refers to a folk and traditional medicinal practice based on the use of plants and plant extracts. In essence, herbalism is the practice of herb-based care and pharmacognosy is the scientific study of herbs with medicinal purposes. Within the practice of herbalism there are a variety of different traditions including, for example, traditional Chinese medicine or the Indian ayurvedic medicine. Each of these has a unique paradigm on health, illness, and disease. Unlike pharmacognosists, herbalists are not particularly interested in specific active constituents found within a plant. Instead, they focus on the healing properties of the plant or part of plant (seed, root, leaf, etc.) and how it will benefit the body to heal itself. Although non-herbalists may also use herbal medicines in their clinical practice, they likely do so under a different health paradigm. Homeopaths also have a holistic approach to health, but their material medica uses a 'like cures like' philosophy of treating patients with ultra-dilute formulations unlikely to contain significant (if any) 'active' ingredient. **Homeopathy**, then, is unlike herbal medicine, herbalism, or pharmacognosy. It has not been included in this text.

The current trend in natural product use follows many different health paradigms – some are popular because of their use in traditional Chinese medicine or Ayurveda, some from the widespread use of herbal medicine in Europe, and some due to increasing published studies on natural medicines, somewhat representative of the renewed interest in pharmacognosy. So, irrespective of the

particular health paradigm from which the natural health products summarized in this text are derived, we will adopt the pharmacology perspective (or perhaps in this case, pharmacognosy would be the more accurate term). As such, individual constituents (chemical entities) of each natural product are discussed with regard to their pharmacologic or toxicologic properties. Since this likely represents a new vocabulary for most healthcare professionals, some common classes of herbal constituents are described below.

Glossary of terms used in natural product pharmacology (**pharmacognosy**)

A true understanding of the nature of plant constituents demands a solid foundation in organic chemistry since many constituent names are based on the compound's chemical structure. An explanation of the structure–function relationship of plant constituents is beyond the scope of this text. Whenever possible, chemical constituents will be described here by their pharmacologic function or unique physicochemical properties rather than their structural forms. However, more often than not, the constituents derived from plants are grouped according to their structural similarity rather than functional effect. In these cases, the chemistry is simplified such that undergraduate level organic chemistry knowledge will suffice. Further details can be found in the texts recommended at the end of this chapter.

Alkaloids are chemicals formed from amino acids. True alkaloids contain a heterocyclic ring structure containing nitrogen while proto alkaloids do not have the nitrogen in the ring. Pseudo-alkaloids are related compounds that contain a heterocyclic ring structure containing nitrogen but are not derived from amino acids. Alkaloids are highly reactive substances with biologic activity in low doses. In plants, most alkaloids (which are bases) form salts with acids. Alkaloids may be monocyclic, bicylic, or polycylic. Alkaloids may occur as pyridine-piperidines, tropanes, quinolines, isoquinolines, indoles, imidazoles, steroidals, purine bases, and alkaloidal amines. Drug examples of alkaloids include atropine, ipecac, nicotine, colchicine, caffeine, theophylline, quinine, vinblastine, tubocurarine, reserpine, yohimbine, morphine, and the ergot alkaloids. They are usually bitter-tasting white solids (although nicotine is a brown liquid). Apart from their similar structural roots, alkaloids are not related and thus do not necessarily share any pharmacologic properties.

Anthocyanins are plant pigments that strongly absorb in the ultraviolet (UV) spectrum and thus have a role in attracting insects (by carnivorous plants or for pollination purposes) as well as UV protection. Plants containing anthocyanins can be of a variety of colors. They are usually red, purple, or blue but depending on their oxidation state may even be yellow or colorless. Over 300 different anthocyanins have been identified in plants. They are one class of flavonoid compounds that are very popular today due to their possible health benefits as antioxidants. The most popular supplements are grape seed extract, pine bark extract, and green tea. Anthocyanin-containing plants have also been used historically as anti-inflammatories and for enhancing vision. Cranberries, bilber-

ries, apples, eggplant, and radish all contain anthocyanins. Anthocyanins also contribute to the color changes of leaves in autumn.

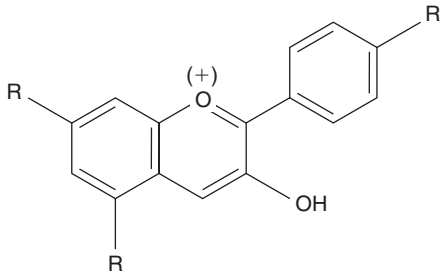


Figure 2.1 Basic structure of anthocyanins.

Anthraquinones have a three-ring structure and have been used for centuries as purgatives and dyes. They are usually found in plants in a glycoside form (i.e. attached to sugar molecules). Anthraquinone laxatives irritate the bowel wall, provoking increased muscle contractions and peristaltic movements. Examples include senna, cascara sagrada, rhubarb, yellow dock, and aloe. Anthraquinones may also have antiviral, antibacterial, and cytotoxic properties.

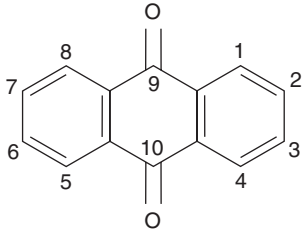


Figure 2.2 Basic structure of anthraquinones.

Coumarins are derived from cinnamic acid and are usually found in grasses and the pea family (such as clover). Coumarins are responsible for the scent of fresh cut grass. Dicumarol, the fermentation product of coumarin that is thought to inhibit vitamin K effects on coagulation biosynthesis due to its similarity in structure to vitamin K, is the anticoagulant from which warfarin was synthesized. Many coumarins, if injected, are anticoagulants but most plant coumarins are neutralized in the digestive tract and so have very little anticoagulant effects when ingested. Derivatives of coumarins have antifungal properties (like umbelliferone from the parsley family) and vascular tone effects (like esculin from horse chestnut).

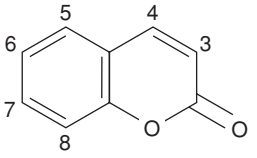


Figure 2.3 Basic structure of coumarins.

Flavonoids are commonly found as pigments in flowering plants. Over 2000 different flavonoid compounds have been found in plants in either the free state or as glycosides. They are polyphenolic compounds with a base structure that consists of two aromatic rings joined with a three-carbon chain – the so-called 'C6-C3-C6' carbon skeleton. The three-carbon chain may be part of a more complex structure including ringed moieties. The nature of the functional groups at this central complex determines the subclass of flavonoids. Some examples include flavones (such as apigenin found in celery and other herbaceous plants of the *Labiatae*, *Umbelliferae*, and *Compositae* families), flavonols (found in woody flowering plants like quercitol or kaempferol from *Sambucus nigra*), flavonones, and anthocyanins. Flavonoids found in colorful fruits and vegetables have powerful antioxidant properties. Flavonoids are the reason why green tea, grape seed extract and pine bark extract have been so popular over the past few years.

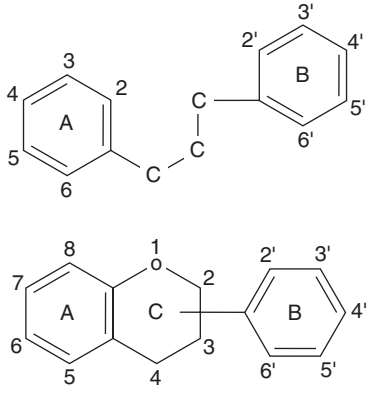


Figure 2.4 Two variants of the basic structure of flavanoids.

Isoflavonoids are similar in structure to flavonoids but have one of their benzene rings at a slightly different position. Unlike most flavonoids, isoflavonoids are colorless and are limited to legume plants. Soy isoflavones are touted as agents that may lower low-density lipoprotein (LDL) cholesterol and triglycerides as well as helping with menopausal symptoms and complications.

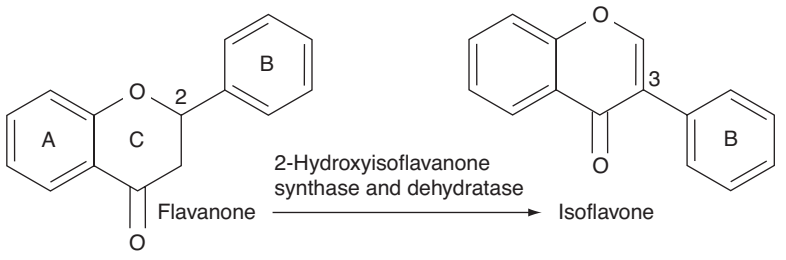


Figure 2.5 The conversion of flavonone to isoflavone.

Glucosinolates is a term often used to refer to a group of bound toxins such as the cyanogenic and isothiocyanate glycosides. Some glycosides produce hydrocyanic acid when hydrolyzed. These are referred to as **cyanogenic glycosides**. Amygdalin, found in apricot pits and bitter almonds, or prunasin, found in wild cherry bark, for example, are cyanogenic glycosides. The hydrolysis of the glycoside sinigrin from plants in the mustard family leads to allyl isothiocyanate – mustard oil. Plants from the mustard family as well as the cyanogenic glycosides have been used due to their anticarcinogenic properties. Laetrile (amygdalin) was a very popular cancer remedy in the 1980s despite clinical evidence of a lack of effect. Unfortunately, after pure amygdalin was banned, patients tried ingesting large amounts of apricot kernels, which led to several deaths because apricot kernels also contain an enzyme that hydrolyzes amygdalin and releases cyanide. Subsequent research showed that amygdalin alone can lead to cyanide poisoning.

Glycosides are compounds that contain a carbohydrate (glycone) and non-carbohydrate (aglycone) moiety joined by an acetal group. Although their chemical names can be quite complex, they can be recognized from their trivial names which are formed from the source plant name and the suffix '-in' such as salicin which is found in *Salix* (willow). Salicin is an **alcohol glycoside** found in willow bark that yields salicyl alcohol when hydrolyzed. Salicin has anti-inflammatory properties probably due to its oxidation into salicylic acid. It is shown here.

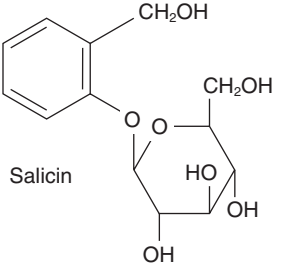
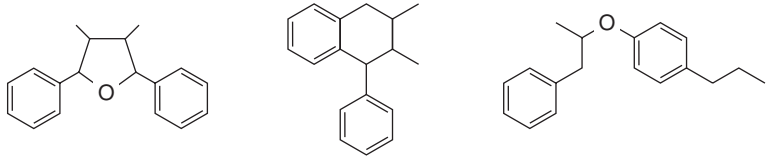


Figure 2.6 Salicin, an example of an alcohol glycoside.

Classification of glycosides is difficult since it can be done either by the sugar or the non-sugar group or by pharmaceutic viewpoint. Glycosides are ubiquitous within plants and their aglycone groups include, among others, tannins, aldehydes, alcohols, saponins, anthraquinones, lactones, flavanols, phenols, and isocyanates. The anthraquinones described earlier are found in plants as glycosides. Glucosinolates, a form of glycoside toxin, are described above. Glucovanillin is an **aldehyde glycoside** that is hydrolyzed to vanillin (an aldehyde) – the principal flavoring constituent of vanilla. Uva ursi, or bearberry, has a long tradition in folk medicine as a urinary antiseptic. Arbutin is a **phenol glycoside** found in bearberry (a small evergreen shrub) that can be hydrolyzed to the phenol hydroquinone – the agent that made arbutin a popular choice for urinary tract infections prior to sulfa antibiotics. Today hydroquinone is commonly used topically as a skin bleacher. The combination of sapogenin and a sugar yields a **saponin glycoside** which is described below as saponin. Sapogenins have steroid or triterpenoid aglycone structures. Cardiac glycosides, like digitoxin, are an example of a sapogenin with a steroid aglycone. These are discussed in greater detail under saponins.

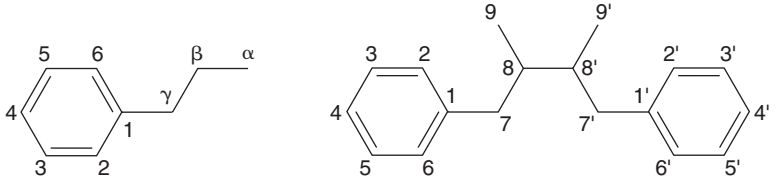
Lignans are plant products formed by the coupling of two para-propylphenol (phenylpropanoid) moieties at their β carbon atoms. The three structures below represent different lignan skeletal types.



(1) (2) (3)

Figure 2.7 Three different skeletal structures of lignans.

If the two C_6C_3 units (**4**) are linked by a β,β′-bond the parent structure lignane (**5**) is used as the basis for naming the lignan.



(4) (5)

Figure 2.8 β-β′-bond linkage of two C_6C_3 units to form a lignan (lignane).

If the two C_6C_3 units (**4**) are linked by a bond other than a β,β′-bond the parent structure, neolignane, is used as the basis for naming the neolignan such as 3,3′-neolignane shown below.

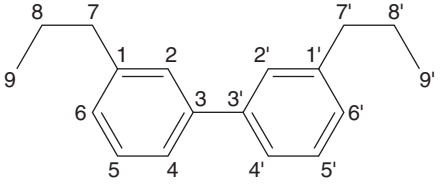


Figure 2.9 Non- β-β′-bond linkage of two C_6C_3 units to form a neolignan (3,3'-neolignane).

Lignans and neolignans play a role in plant defense as they have antimicrobial, antifungal, and insect repellant properties. Podophyllum is the dried rhizome and roots of *Podophyllum peltatum* (also known as mayapple or American mandrake). A resin from podophyllin (called podophyllotoxin) is a lignan that is used topically in the treatment of warts due to its antimitotic properties. The chemotherapeutic drug etoposide is a semisynthetic podophyllotoxin derivative. Podophyllotoxin is also a potent purgative. Other lignans, such as secoisolariciresinol, are considered to be phytoestrogens. Flaxseed has become very popular as a natural product therapy in women's health due to its very high lignan content. Other benefits of flaxseed, such as its potential role in lowering LDL cholesterol, are also attributed to its lignan content. Much of the natural product lay literature incorrectly states that lignans are synonymous with phytoestrogens. The chemical structures, and thus function, of lignans are quite variable. As discussed here, podophyllotoxin, a prototypic lignan, is used for papillomas and not as a phytoestrogen. It is shown here.

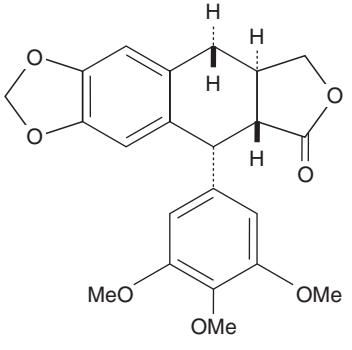


Figure 2.10 Podophyllotoxin, an example of a lignan.

Saponins are compounds that form colloidal solutions in water and foam on shaking. The name comes from the soapwort plant (*Saponaria*) the root of which was used as a soap. They consist of a polycyclic aglycone derived from squalene that is either a choline steroid or a cyclic triterpenoid (see terpenoids for description) attached via C3 and an ether bond to a sugar side chain, thus making them glycosides. Certain saponins called 'sapotoxins' are used as fish poisons. They have even been used in poison arrow tips. When ingested, saponins are usually safe in humans; however, when injected, their detergent effect on the lipid cell membrane leads to hemolysis. A large variety of plants contain saponins. The physiologic effects of saponins depend on the particular aglycone. Saponins from wild yam or fenugreek are precursors to estrogens or progestogens. They also exert lipid-lowering effects. The **cardiac glycosides**, like digitoxigenin from the foxglove plant, have a steroid aglycone group. These agents enhance cardiac contractility by increasing intracellular myocyte calcium concentration through effects on the Na^+/K^+ ATPase pump. Many plants have cardiac glycosides including lily-of-the-valley, Christmas rose, oleander, squill, and ouabain. Glycyrrhizin is a saponin from licorice that has been used as an expectorant and sweetener. When it is hydrolyzed in the body it forms glycyrrhetinic acid which inhibits enzymes that metabolize prostaglandins E2 and F2α. Physiologically, this leads to a reduction in gastric acid secretion and stimulation of uterine smooth muscle. A metabolite of glycyrrhetinic acid can inhibit 11-β-hydroxysteroid dehydrogenase which converts active cortisol to inactive cortisone in the kidneys. The net effect is sodium and water retention, hypokalemia, and hypertension. Ginseng contains a mixture of triterpenoid saponins, several of which are steroidal triterpenes called ginsenosides. These are thought to be responsible for ginseng's biologic properties. The skeleton structure for the triterpenoid saponins of ginseng (ginsenosides) is shown below.

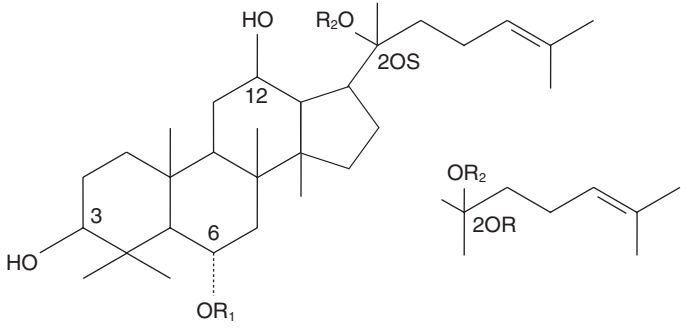


Figure 2.11 Typical skeletal structure of triterpenoid saponins found in ginseng (ginsenosides).

Tannins are plant polyphenols that contain hydroxyl or carboxyl groups that can form strong complexes with proteins. The ability of tannins to precipitate

proteins enables the conversion of animal hides to leather. Tannins are also responsible for the 'puckering' taste of red wine or unripe fruit. Tannins are broadly categorized into two forms – hydrolyzable and non-hydrolyzable.

Hydrolyzable tannins have a polyol (like D-glucose) central core and hydroxyl groups that are esterified with phenolic compounds. Hydrolyzable tannins are usually present in low amounts in plants. Tannins can combine with proteins and make them resistant to proteolytic enzymes. When used in living tissues this action is referred to as an 'astringent' effect. Astringents have historically been applied topically to burns and wounds or taken internally for gastrointestinal tract disorders like ulcers or gastritis. When superficial proteins in exposed tissues are precipitated, a protective and mildly antiseptic coat is thought to form that enables regeneration of tissue to occur below. The astringent effects of tannins from witch hazel leaves or nutgall have been known for centuries. A typical polymer of gallic acid is shown below. Tannic acid is a polymer of about eight monomers of gallic acid and glucose.

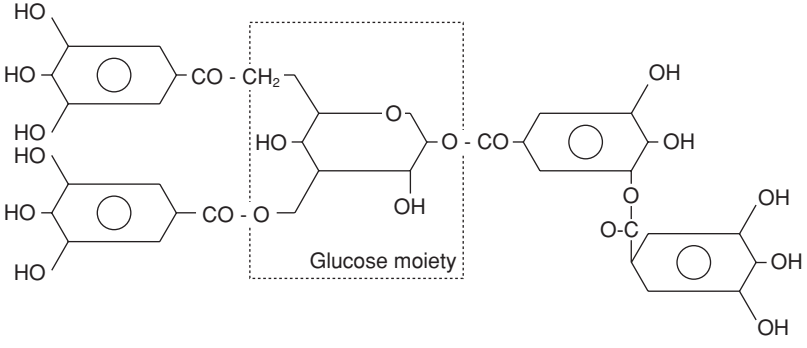


Figure 2.12 Structure of a hydrolyzable tannin formed as a polymer of gallic acid with a polyol (glucose moiety) at the core.

Non-hydrolyzable tannins (also called condensed tannins based on their small molecular size) are composed of flavonoid units linked by carbon-to-carbon bonds that cannot be cleaved by hydrolysis. When non-hydrolyzable tannins are heated in acidic solutions they form anthocyanidin pigments (described earlier) leading to their other synonym, proanthocyanidins. Proanthocyanidins (also referred to as pycnogenols) lead to anthocyanidins that are effective antioxidants and free radical scavengers. As discussed earlier, they are found in pine bark, grape seed, and green tea. A trimer of catechin is shown here.

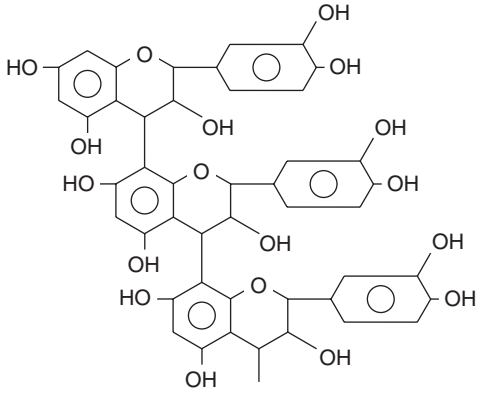


Figure 2.13 Structure of a non-hydrolyzable tannin formed as a trimer of catechin without a polyol at its core.

Terpenes and terpenoids are synthesized from a 5-carbon isoprene molecule (C_5H_8). Terpenes are hydrocarbons and terpenoids are oxygen-containing hydrocarbons. Since all these molecules are made from isoprene, they can also be called isoprenoids. Two isoprene units form a 10-carbon molecule called a monoterpene. Terpenoids can be classified based on the number of isoprene units (hence carbons) that make up their skeleton structure. These are summarized in the table below:

Table 2.1 Nomenclature of terpenoids

Terpenoid	*Isoprenes*	*Formula*	*Example*
Monoterpenoids	2	$C_{10}H_{16}$	Cineole (found in eucalyptus)
Sesquiterpenoids	3	$C_{15}H_{24}$	Valerenic acid (found in valerian)
Diterpenoids	4	$C_{20}H_{32}$	Taxol (from Pacific yew)
Triterpenoids	6	$C_{30}H_{48}$	Glycyrrhetic acid (from licorice)
Tetraterpenoids	8	$C_{40}H_{60}$	Lycopene (carotenoids)

A subgroup of structurally related sesquiterpenes are limited to only few families of plants such as *Asteraceae*. These are called **sesquiterpene lactones** and usually are responsible for the bitter taste and toxicity of many plants in which they are found. Artemisinin, a sesquiterpene lactone from *Artemisia annua* has a long history of use for its antimalarial properties. Parthenolide is a sesquiterpene lactone found in feverfew which has been shown to reduce the frequency and severity of migraine. Many triterpenoids exist as pentacyclic structures resembling steroid skeletons. Others have a tetracyclic structure. Since most are alcohols they can combine with sugars to form glycosides. Pentacyclic triterpenoids are often saponins. Carotenoids are found in brightly colored fruits and vegetables. Lycopene and other carotenoids are powerful antioxidants.

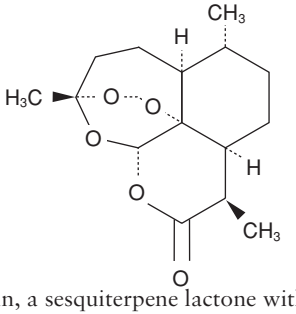


Figure 2.14 Artemisinin, a sesquiterpene lactone with antimalarial properties.

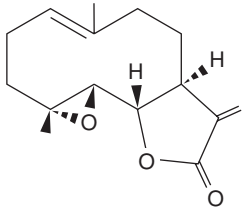


Figure 2.15 Parthenolide, a sesquiterpene lactone found in feverfew.

Volatile oils are the fragrant or aromatic plant compounds that evaporate when exposed to air at normal temperatures. They are also called essential oils as these oils impart the odoriferous character or 'essence' of the plant. Spices are made from plant parts that contain volatile oils. Volatile oils are also used in aromatherapy, as flavoring agents, and in the perfume industry. Volatile oils may also have medical properties such as the antiseptic or expectorant properties of eucalyptus oil or disinfectant properties such as pine oil. Structurally, volatile oils are either terpenoid derivatives (like those volatile oils characteristic of menthol, camphor, lemon and pine) or phenylpropanoids (like those in cinnamon, cloves, and wintergreen).

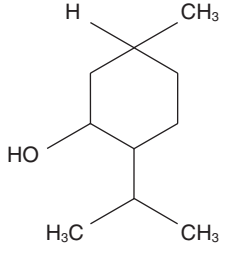


Figure 2.16 Menthol, a volatile oil and terpenoid derivative.

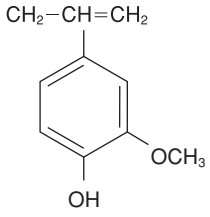


Figure 2.17 Eugenol (from cloves)

Suggested reading

Bisset NG, Wichtl M, eds. Herbal Drugs and Phytopharmaceuticals. Boca Raton: CRC Press, 1994.

Bruneton J. Pharmacognosy: Phytochemistry Medicinal Plants, 2nd ed. Hampshire, UK: Intercept, 1999.

Dewick PM. Medicinal Natural Products: A Biosynthetic Approach. Chichester: John Wiley and Sons, 1997.

Evans WC. Trease and Evans Pharmacognosy, 14th ed. London: WB Saunders Company Ltd, 1996.

Heinrich M, Barnes J, Gibbons S, Williamson EM. Fundamentals of Pharmacognosy and Phytotherapy. Edinburgh: Churchill Livingstone, 2004.

Huang KC. The Pharmacology of Chinese herbs, 2nd ed. Boca Raton: CRC Press, 1999.

Robbers JE, Speedie MK, Tyler VE. Pharmacognosy and Pharmacobiotechnology. Baltimore: Williams and Wilkins, 1996.

Chapter 3
METHODOLOGY

In keeping with the principles of evidence-based practice, we have endeavored to identify all the relevant literature on the specific health products examined. Our search strategy employed systematic searching of the following databases:

- AltHealthWatch
- AMED
- CinAhl
- Cochrane Database of Systematic Reviews
- Cochrane CENTRAL Controlled Trials Database
- E-Psyche
- DARE
- MedLine

The MeSH terms used for searching included 'pregnancy', 'lactation', and 'breastfeeding'. For individual health products, we searched using both the common and Latin names, and where appropriate, we searched using known synonyms. In the case of a well-known active ingredient or constituent, this term was also used in the search for its safety during pregnancy and lactation. The principal databases used were:

- Pubmed
- Cochrane Trial Registry (CENTRAL) and Cochrane Review database
- AMED
- CINAHL
- E-Psyche

To ensure that reports, trials, and other forms of evidence were not overlooked owing to the variety of common names for each individual herb, e.g. *Panax ginseng* is also known as ren shen in traditional Chinese medicine, the following additional databases were consulted:

- www.naturalstandard.com
- www.naturaldatabase.com
- The Complete German Commission E Monographs by the American Botanical Council

Each relevant journal article was collected and referenced in our database. The nature of the findings and the grade of evidence were then assessed and compiled in our final report.

The grade of evidence for indications was evaluated as follows:

Grade	*Level of evidence*
A	Very strong scientific evidence Statistically significant evidence of benefit from one or more systematic reviews or meta-analyses
B1	Strong scientific evidence Statistically significant evidence of benefit from one or more properly conducted randomized controlled trials (RCTs).
B2	Good scientific evidence Statistically significant evidence of benefit from one or more RCTs. The RCTs, however, are either of small sample size or have discrepancies in their methodologies
C	Fair scientific evidence Statistically significant evidence of benefit from one or more cohort studies or outcome studies
D	Weak scientific evidence Evidence from case series
E	Theoretical and/or clinical evidence Evidence from case reports or expert opinion or laboratory studies
F	Historical or traditional evidence Historical or traditional evidence of use by medical professionals, herbologists, scientists or aboriginal groups

The level of evidence for harm was evaluated as follows:

Level	*Evidence*
1a	Very strong scientific evidence Statistically significant evidence from one or more systematic reviews or RCTs
1b	Strong scientific evidence Statistically significant evidence from one or more cohort studies or control studies
1c	Good scientific evidence Evidence from one or more case series
2	Fair scientific evidence Evidence based on case reports
3	In vitro scientific evidence Evidence based on scientific studies conducted on animals, insects or microorganisms, or laboratory studies on human cells
4	Theoretical evidence Evidence based on scientific theory or expert opinion
5	Unknown No available information

Chapter 4
HERBAL MEDICINES

Herbal medicines are increasingly popular among the general public, particularly women of childbearing age. These medicines are not only viewed as having clinical benefits but are also generally believed to be safe. In some cases, a systematic review of the evidence-based medicine literature shows that this is not the case.

In pregnancy, soon-to-be mothers are concerned about all medications that may affect their health, the health of their fetus, and the pregnancy outcome. When it comes to the types of evidence for herbal medicines during pregnancy and lactation, not all evidence is created equally. The type of evidence for the safety of herbal medicines during pregnancy and lactation ranges from theoretical to animal studies, to case reports, to cohort studies and finally to randomized controlled trials.

This chapter aims to provide healthcare practitioners and mothers-to-be with the best available evidence-based safety information on the products they may choose to use or not to use during pregnancy and lactation. We selected 60 herbal medicines in total. In choosing these herbs, we set forth a number of selection criteria. These are outlined below.

Herbs that are frequently used during pregnancy, e.g. black and blue cohosh, red raspberry, evening primrose oil
Herbs that are used to treat pregnancy-related complaints, e.g. ginger
Herbs that are known abortifacients, e.g. pennyroyal, parsley
Herbs that have narrow therapeutic indices and are toxic, e.g. digitalis, deadly nightshade, ephedra
Herbs that are used more often by women than men, e.g. red clover, don quai
Herbs that are known to have hormonal effects, e.g. chastetree
The most frequently used herbs, e.g. St. John's wort (depression), garlic (hyperlipidemia), ginkgo (memory), Echinacea (immune system)

Systematic reviews on all 60 herbal medicines are presented as follows:

Common name
The name by which the herb is commonly referred to, e.g. garlic.

Latin name
The Latin name (genus, species) of the herb, e.g. *Allium sativum*. In some cases, more than one species of the herb has the same therapeutic effect, e.g. *Panax* spp.

Synonyms
Other names by which the herb may be known.

Indications
The main therapeutic indications for the herb. According to evidence-based medicine principles, the indications for the herb are evaluated based on grades/levels of evidence (see Chapter 3).

Pregnancy
The safety of the herb during pregnancy. According to evidence-based medicine principles, the safety of the herb during pregnancy is evaluated based on grades/levels of evidence (see Chapter 3).

Lactation
The safety of the herb during lactation. According to evidence-based medicine principles, the safety of the herb during lactation is evaluated based on grades/levels of evidence (see Chapter 3).

Contraindications
Conditions and diseases in which the herb should not be taken.

Caution
Conditions or diseases in which the herb should be used with caution.

Constituents
The main pharmacological constituents in the herb.

Toxicity
The toxicity of the herb (lethal dose (LD_{50}) where available).

Pharmacology
General pharmacological properties of the herb.

Drug interactions
Drugs that may interact with the herb.

Parts used
The part that provides the therapeutic benefits of the herb, e.g. root, leaf, stem.

ALFALFA
Medicago sativa

Synonyms/common names/related compounds[1]
Feuille de luzerne, lucerne, medicago, phytoestrogen, purple medick

Indications

Menopausal symptoms (with sage):[2]	Evidence grade B2
Elevated cholesterol:[3–5]	Evidence grade D
Atherosclerosis:[6,7]	Evidence grade E
Diabetes:[8,9]	Evidence grade E

Pregnancy

Estrogenic activity:[10–13]	Evidence level 3

A study on the effects of dietary genistein exposure during development found that dietary genistein produced effects in multiple estrogen-sensitive tissues in both male and female rats.[10] Another study reported estrogenic activity of genistein and daidzein in human cells in vitro and in rats.[11] The phytoestrogen coumestrol, contained in alfalfa, was reported to be 35 times more potent than the phytoestrogens genistein, biochanin A, formononetin and daidzein.[12] A review article on the potential value of plants as sources of anti-fertility agents reported that alfalfa has estrogenic activity.[13]

Isolated compounds have uterine-stimulating activity:[14]	Evidence level 4

A review article on the potential value of plants as sources of anti-fertility agents reported that alfalfa was a uterine stimulant and that its constituent stachydrine was a uterine stimulant.[14]

Emmenagogue:[15]	Evidence level 4

A herbal medicine compendium reported that alfalfa is an emmenagogue.[15] There are no reports in the scientific literature of alfalfa being an emmenagogue.

Anti-gonadotrophic activity:[14]	Evidence level 4

A review article on the potential value of plants as sources of anti-fertility agents reported that alfalfa had anti-gonadotrophic activity in rats where the acid extract interfered with the growth of the seminal vesicles and potentiated the action of estrogens.[14]

Consumed as food

Minimal risk:[15–18]	Evidence level 3

In a study on the effects of alfalfa feeding on pregnancy and lactation in beef heifers, no adverse effects were reported when alfalfa was consumed in food amounts.[16] A herbal medicine compendium reported that when consumed as food, alfalfa is believed to be of minimal risk.[15]

Lactation

Estrogenic activity:[10–12]	Evidence level 3

A study on the effects of dietary genistein exposure during development found that dietary genistein produced effects in multiple estrogen-sensitive tissues in both male and female rats.[10] Another study reported estrogenic activity of genistein and diadzein in human cells in vitro and in rats.[11] The phytoestrogen coumestrol, contained in alfalfa, was reported to be 35 times more potent than the phytoestrogens genistein, biochanin A, formononetin and daidzein.[12]

Lactogenic:[14]	Evidence level 4

A review article on the potential value of plants as sources of anti-fertility agents reported that alfalfa seeds may be lactogenic.[14]

Consumed as food

Minimal risk:[15–17]	Evidence level 3

In a study on the effects of alfalfa feeding on pregnancy and lactation in beef heifers, no adverse effects were reported with alfalfa consumed in food amounts.[16] A herbal medicine compendium reported that when consumed as food, alfalfa is believed to be of minimal risk.[15]

Contraindications

Systemic lupus erythematosus[19,20]

Caution

- Hormone sensitive conditions such as breast, uterine, or ovarian cancer, endometriosis and fibroids[12,21]
- Diabetes [15]

Constituents

- Saponins[15,22]
- Flavonoids[23]
- Phytoestrogens:[1,12,24] coumestrol, genistein, biochanin A, and daidzein
- Vitamins A, C, E, and K[15]

- Manganese[15,25]
- Stachydrine[14]

Toxicity

In a 6-week study, no signs of toxicity were reported in six humans consuming 160 g a day of alfalfa for 3 weeks followed by 80 g of alfalfa a day for 3 weeks.[5]

Pharmacology

- The phytoestrogens coumetrol, genistein, biochanin A and daidzein have been shown to have estrogenic properties.[10–12,24]
- The saponin constituents in alfalfa leaves were shown to decrease total cholesterol levels without affecting high-density lipoprotein levels.[15]
- Alfalfa constituents may decrease cholesterol absorption and increase fecal excretion of neutral steroids and bile acids.[15,26]
- Alfalfa contains manganese which might be responsible for its hypoglycemic effects.[15]
- Alfalfa contains medicagol, which appears to have anti-fungal properties.[1]

Drug interactions[1]

Anti-coagulants[15]
Photosensitizing drugs[27]
Oral contraceptives[1,15]
Hormone therapy[15]
Warfarin (Coumadin)[15]

Parts used

Above ground parts[28]

References

1. Jellin JM, Batz F, Hitchens K. Natural Medicines Comprehensive Database, 3rd ed. Stockton, CA: Therapeutic Research Faculty, 2002:1530.
2. De Leo V, Lanzetta D, Cazzavacca R, Morgante G. [Treatment of neurovegetative menopausal symptoms with a phytotherapeutic agent]. Minerva Ginecol 1998; 50:207–211.
3. Malinow MR, Connor WE, McLaughlin P et al. Cholesterol and bile acid balance in Macaca fascicularis. Effects of alfalfa saponins. J Clin Invest 1981; 67:156–162.
4. Molgaard J, von Schenck H, Olsson AG. Alfalfa seeds lower low density lipoprotein cholesterol and apolipoprotein B concentrations in patients with type II hyperlipoproteinemia. Atherosclerosis 1987; 65:173–179.
5. Malinow MR, McLaughlin P, Stafford C. Alfalfa seeds: effects on cholesterol metabolism. Experientia 1980; 36:562–564.
6. Malinow MR. Experimental models of atherosclerosis regression. Atherosclerosis 1983; 48:105–118.
7. Malinow MR, McLaughlin P, Naito HK, Lewis LA, McNulty WP. Effect of alfalfa meal on shrinkage (regression) of atherosclerotic plaques during cholesterol feeding in monkeys. Atherosclerosis 1978; 30:27–43.

8. Swanston-Flatt SK, Day C, Bailey CJ, Flatt PR. Traditional plant treatments for diabetes. Studies in normal and streptozotocin diabetic mice. Diabetologia 1990; 33:462–464.
9. Gray AM, Flatt PR. Pancreatic and extra-pancreatic effects of the traditional anti-diabetic plant, Medicago sativa (lucerne). Br J Nutr 1997; 78:325–334.
10. Delclos KB, Bucci TJ, Lomax LG et al. Effects of dietary genistein exposure during development on male and female CD (Sprague-Dawley) rats. Reprod Toxicol 2001; 15:647–663.
11. Casanova M, You L, Gaido KW et al. Developmental effects of dietary phytoestrogens in Sprague-Dawley rats and interactions of genistein and daidzein with rat estrogen receptors alpha and beta in vitro. Toxicol Sci 1999; 51:236–244.
12. Elakovich SD, Hampton JM. Analysis of coumestrol, a phytoestrogen, in alfalfa tablets sold for human consumption. J Agric Food Chem 1984; 32:173–175.
13. Farnsworth NR, Bingel AS, Cordell GA, Crane FA, Fong HH. Potential value of plants as sources of new anti-fertility agents II. Pharm Sci 1975; 64:717–753.
14. Farnsworth NR, Bingel AS, Cordell GA, Crane FA, Fong HH. Potential value of plants as sources of new anti-fertility agents I. J Pharm Sci 1975; 64:535–598.
15. Newall CA, Anderson LA, Phillipson JD. Herbal Medicines: A Guide for Health-care Professionals. London, UK: Pharmaceutical Press, 1996:296.
16. Vanzant ES, Cochran RC, Johnson DE. Pregnancy and lactation in beef heifers grazing tallgrass prairie in the winter: influence on intake, forage utilization, and grazing behavior. J Anim Sci 1991; 69:3027–3038.
17. Coffey KP, Paterson JA, Saul CS et al. The influence of pregnancy and source of supplemental protein on intake, digestive kinetics and amino acid absorption by ewes. J Anim Sci 1989; 67:1805–1814.
18. Guay KA, Brady HA, Allen VG et al. Matua bromegrass hay for mares in gestation and lactation. J Anim Sci 2002; 80:2960–2966.
19. Malinow MR, Bardana EJ Jr, Pirofsky B, Craig S, McLaughlin P. Systemic lupus erythmatosus-like syndrome in monkeys fed alfalfa sprouts: role of a nonprotein amino acid. Science 1982; 216:415.
20. Roberts JL, Hayashi JA. Exacerbation of SLE associated with alfalfa ingestion. N Engl J Med 1983; 308:1361.
21. Kurzer MS, Xu X. Dietary phytoestrogens. Annu Rev Nutr 1997; 17:353–381.
22. Malinow MR, McLaughlin P, Stafford C et al. Comparative effects of alfalfa saponins and alfalfa fiber on cholesterol absorption in rats. Am J Clin Nutr 1979; 32:1810–1812.
23. Stochmal A, Piacente S, Pizza C et al. Alfalfa (Medicago sativa L.) flavonoids. 1. Apigenin and luteolin glycosides from aerial parts. J Agric Food Chem 2001; 49:753–758.
24. Leung AY, Foster S. Encyclopedia of Common Natural Ingredients Used in Food, Drugs and Cosmetics. New York, NY: John Wiley & Sons, 1996:649.
25. Rubenstein AH, Levin NW, Elliott GA. Manganese-induced hypoglycemia. Lancet 1962:1348–1351.
26. The Review of Natural Products by Facts and Comparisons. St. Louis, MO: Wolters Kluwer Co., 1999.
27. Brown R. Potential interactions of herbal medicines with anti-psychotics, anti-depressants and hypnotics. Eur J Herbal Med 1997; 3:25–28.
28. Brinker F. Herb Contraindications and Drug Interactions. Sandy, OR: Eclectic Medical Publications, 2001:432.

ALOE
Aloe spp.

Synonyms/common names/related substances[1]

A. vera (A. barbadensis), A. ferox, A. africana, A. arborescens natalenis, A. capensis, A. leaf gel, *A. perfoliata, A. perryi, A. spicata*, salvia, cape aloes, Barbados aloe, Curacao aloe, hepatic aloes, aloe dried juice from leaf, aloe juice, burn plant, elephant's gall, hsiang-dan, lily of the desert, lu-hui, miracle plant, plant of immortality

Indications

Oral

Chronic constipation:[2–6]	Evidence grade B1
Solid tumors (with melatonin):[7]	Evidence grade C
Elevated cholesterol and triglycerides, hyperglycemia and low high-density lipoprotein cholesterol (with husk of Isabgol):[8]	Evidence grade C
Chronic venous leg ulcers:[9]	Evidence grade C
Fibromyalgia, chronic fatigue syndrome:[10]	Evidence grade C
Diabetes type 2:[11–13]	Evidence grade E
Bronchial asthma (aloe vera gel):[14]	Evidence grade E

Topical

Psoriasis vulgaris:[15]	Evidence grade B1
Herpes simplex type II:[16,17]	Evidence grade B1
Seborrheic dermatitis:[18]	Evidence grade B1
Radiation induced dermatitis:[19]	Evidence grade B2
Occupational dry skin, irritant contact dermatitis:[20]	Evidence grade B2
Burn wounds:[21]	Evidence grade C
Alveolar osteitis:[22]	Evidence grade C

Chronic venous leg ulcers:[9]	Evidence grade C
Anti-arthritic, anti-inflammatory (*A. africana*):[23]	Evidence grade E
Anti-inflammatory (*A. vera*):[24]	Evidence grade E
Wounds (*A. vera*):[24,25]	Evidence grade E

Pregnancy

Oral

Potentially nephrotoxic:[26]	Evidence level 2
Potential hepatic dysfunction:[26]	Evidence level 2

A case of acute oliguric renal failure and liver dysfunction was reported in the literature following traditional therapeutic use of cape aloes.[26]

Potential abortifacient:[27]	Evidence level 4
Emmenagogue:[27]	Evidence level 4

A review article on the potential value of plants as sources of anti-fertility agents reported that aloe species are potential abortifacients and emmenagogues.[27]

Potentially genotoxic:[3,28,29]	Evidence level 3
Potentially mutagenic:[3,28,29]	Evidence level 3
Potentially carcinogenic:[3,28,29]	Evidence level 3

Aloe-emodin, a 1,8-dihydroxyanthraquinone found in aloe, is potentially carcinogenic, mutagenic and genotoxic in mice.[3,28,29]

Topical

Aloe vera gel – minimal risk:[3,30]	Evidence level 4

A herbal medicine compendium reported that the external use of aloe vera gel is not a concern during pregnancy. The external use of aloe was not reported in the scientific literature as contraindicated or safe during pregnancy or lactation.

Lactation

Oral

Potentially genotoxic:[3,28,29]	Evidence level 3