Chapter 12

Women and Herbal Medicine

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Introduction: Growth of Herbal Medicine Use

The therapeutic use of botanicals—commonly referred to as phytotherapy and herbal medicine—began thousands of years ago in medicinal practices around the world and has recently gained popularity in Western medicine. Herbal medicine is now considered an integral part of health care on a global scale. For many nations, herbal medicine is considered to be the first-line therapy; up to 50% of medicinals in China are traditional herbals, and for more than half of the children in African nations such as Nigeria and Ghana, the World Health Organization (WHO) reported that herbs are considered first-line therapy for malaria-related fevers. In the United States, a 2007 National Center for Complementary and Alternative Medicine (NCCAM) and the Centers for Disease Control and Prevention (CDC) joint survey indicated that 38% of adults use complementary and alternative medicine (CAM), with natural and herbal remedies being the most prominent modality (http://nccam.nih.gov/news/camstats/2007).

Over the past 50 years, there has been a steady growth of herbal medicine users in the United States (Kessler et al., 2011), predominated by middle-aged women (Tindle, Davis, Phillips, & Eisenberg, 2005). These women use herbs in a variety of conditions such as premenstrual syndrome (PMS), pregnancy-induced nausea and vomiting, insomnia, urinary tract infections (UTIs), menopausal symptoms (Posadzki et al., 2013), fertility enhancement (Rayner, Willis, & Burgess, 2011), and depression (Wu et al., 2007).

With high demand for herbal remedies, this multibillion dollar industry has grown steadily in the past decade, with many individual herbs grossing over $10 million annually (Lindstrom, Ooyen, Lynch, & Blumenthal, 2013). These products are no longer found only on the shelves of specialty natural products stores, but they appear in chain drug stores and supermarkets, with labels promoting the products as "natural," providing consumers with a relative sense of safety (Ernst, 1998). The increase in access to herbal remedies and their sales were mainly initiated with the Dietary Supplement Act of 1994, an amendment to the Federal Food, Drug, and Cosmetic Act, which does not require companies to obtain FDA approval for a dietary supplement before marketing it.

The ubiquity and general positive perception of herbal medicines—along with the growing trend of CAM and herbal medicine use in the United States—make it likely for health professionals to regularly care for patients who will be taking a variety of herbal remedies. Therefore, it is critical for health-care providers to be more informed about

herbal medicines. There is a general assumption among herbal users that Western-trained clinicians are either opposed to or lack knowledge of phytotherapy (Blendon, DesRoches, Benson, Brodie, & Altman, 2001) and other forms of CAM (Robinson & McGrail, 2004), which leads to nondisclosure of herb use by as many as 67% of patients (Mehta, Gardiner, Phillips, & McCarthy, 2008) that can potentially result in herb–drug and herb–disease interactions. It is important that the clinician be aware of any herbal medicines the client is taking as they may interact with other medicines being prescribed by the clinician. Therefore, it is crucial for clinicians to inquire of their patients about any herbal use practices in order to avoid such interactions that could possibly compromise their patients' health.

Disclaimer: Many herbal users have reported using CAM therapies because of media influence (Wu et al., 2007), which is often not evidence-based. Even if a herb is deemed safe to treat a particular ailment—as reported in randomized clinical trials—it still runs the risk of interacting with pharmaceuticals adversely, containing contaminants such as heavy metals and pyrrolizidine alkaloids, or of being consumed incorrectly owing to obfuscated marketing (Bent, 2008). Clinicians should also pay attention to the quality of the studies and funding source. Another major issue with studies on herbal remedies is the lack of consistency among the products and lack of standardization of the herbs used in clinical trials.

The purpose of this chapter is to present a brief overview of seven selected herbal medicines that are either commonly used or are emerging in popularity in their use for common female ailments. Although the selected herbs may have some scientific evidence to support their use, their immediate substitution for pharmaceuticals may not be warranted. Even when a herbal remedy is deemed to be an appropriate therapy based on centuries of observed efficacy in traditional medical practices, the quality of the herbal supplements should be scrutinized in view of lack of regulation by the FDA (Ernst, 1998). Although the FDA does not regulate the manufacturing processes of the herbal supplements like pharmaceuticals, herbal supplements manufacturers can have their products and their manufacturing processes evaluated by the United States Pharmacopeial Convention (USP), which assesses the quality, strength, and even labeling of dietary supplements. The request for increased manufacturing transparency and potential verification by the USP does provide a greater level of credibility to herbal medicine because the USP standards are enforceable by the FDA and other government agencies (usp.org). Furthermore, certain herbs have conflicting evidence in regard to efficacy and safety, which may be partly because of the bioactive complexity inherent in the herbs, poor research methodology of published studies, or the use of nonstandardized materials. The herbs selected for presentation in this chapter are discussed in relation to the condition/ailment for which there is evidence to support their use. The seven herbs described are St. John's wort, kava, *Rhodiola rosea*, cranberry, chasteberry, black cohosh, and valerian.

In presenting each herb, the aims are to discuss

1. The ailment for which it is used
2. Scientific evidence for its use
3. Potential mechanisms of action
4. Side effects and drug interactions
5. Dosage

The data presented in this chapter is derived from an extensive literature review. A number of databases such as Webofknowledge, Natural Comprehensive Medicine, Natural Standard, American Botanical Council, and Cochrane were utilized in identifying

the most researched herbs used in women's health. Owing to space constraints, remedies for ailments without female gender predominance—influenza, nausea, headaches, for example—were not considered. An initial search of the topic "herb" and containing "women" in the title furnished several hundred studies and reviews from Webofknowledge, 85 of which were relevant. Reviews and studies were compared with database meta-analyses and studies gathered from searching bibliographic references. The final groups of herbs were organized by ailment, with general use and application, potential mechanisms of action, side effects, and drug interactions as factors in determining safety and efficacy.

Ailments and Herbal Treatments

Depression and Anxiety: St. John's Wort, Kava, and Rhodiola rosea

Feelings of anxiety and depression can arise from stress and unfortunate events in life, but should not be present on a daily basis. When the feelings become chronic, such as for a period of 2 weeks or longer (Adaa.org/living-with-anxiety/women), it is considered a disorder. Depression and anxiety are more common in females (Piccinelli & Wilkinson, 2000), with depression being the most prevalent mental health disorder among women (World Health Organization, 2013). Gender disparity in regard to the propensity—as opposed to diagnosis—of depression and anxiety disorders has recently been challenged (Martin, Neighbors, & Griffith, 2013).

St. John's wort and kava are among the most researched herbs for depression and anxiety, respectively. *Rhodiola rosea* is an emerging herb for the treatment of anxiety and depression. While the number of trials is small relative to St. John's wort and kava, multiple studies reveal that *R. rosea* is a promising herbal remedy to manage anxiety and mild depression in women.

St. John's Wort (*Hypericum perforatum*)

Potential Mechanism of Action. St. John's wort is purported to have several potential pharmacological actions to account for its antidepressant function. The phloroglucinol derivative within the *H. perforatum* extract, hyperforin, has been shown to hinder synaptosomal uptake of γ-aminobutyric acid (GABA), noradrenaline, dopamine, l-glutamate, and serotonin (Chatterjee, Bhattacharya, Wonnemann, Singer, & Müller, 1998). This study was completed on rats and utilized methanolic (1.5% hyperforin), ethanolic (4.5% hyperforin), and CO_2 extracts (38.8% hyperforin). While the trial utilized an animal rather than a human model to parallel depression disorders, it demonstrated dose-dependent results that were comparable to imipramine (a tricyclic antidepressant [TCA]). The method by which *Hypericum* extract hinders syntaptosomal uptake of serotonin may be partly or fully explained by hyperforin's ability to elevate sodium [Na+], which is the driving force behind neurotransmitter transport, as demonstrated in *in vitro* experiments (Singer, Wonnemann, & Müller, 1999).

Inhibition of neurotransmitter degrading enzymes, monamine oxidase (MAO) and catechol-o-methyltransferase (COMT), has been demonstrated *in vitro* (Cott, 1997; Suzuki, Katsumata, Oya, Bladt, & Wagner, 1984; Thiede & Walper, 1994), and is purportedly caused by flavonoids, flavone glycosides, xanthone, and other lipid-soluble

compounds of the *H. perforatum* extract (Thiede & Walper, 1994). A good example to compare this *in vitro* mechanism to the mechanism of pharmaceuticals is binding of $GABA_A$, as noted by Cott (1997). Benzodiazepines bind $GABA_A$ and can fix it into a conformation with higher affinity for GABA, bringing a further inhibitory effect of GABA and contributing to sedative and anxiolytic behavioral results. Extrapolating St John's wort inhibition of MAO and COMT in *in vitro* experiments to *in vivo* experiments should only serve as an example of potential translation from *in vitro* to *in vivo*. Recent *in vivo* studies found no significant change in MAO or COMT when *Hypericum* extract was used in animal models, so the mechanism is only applicable to *in vitro* studies currently (Sacher et al., 2011; Schroeder et al., 2004).

Other potential mechanisms include upregulation of serotonin receptors (Teufel-Mayer & Gleitz, 1997) and inhibition of substance P-inducing interleukin-6 synthesis (Fiebich, Höllig, & Lieb, 2001) and of dopamine β-hydroxylase (Kleber, Obry, Hippeli, Schneider, & Elstner, 1999). There is no single mechanistic explanation for the effects of *Hypericum*, but it is also possible that many of the above mechanisms work together on the nervous system.

Evidence. St. John's wort is considered a popular therapy for the management of depression, but the evidence is unclear and inconsistent. This is partly due to varying standardizations of *H. perforatum* extract and severity of dysfunction in subject populations. In the Hypericum Depression Trial Study Group (2002), a randomized placebo-controlled trial of 340 individuals with major depression, LI 160 formulation was used. This formulation is a common preparation with a standardized hypericin content of 0.12% to 0.28% (0.72 to 0.96 mg in 900 mg dose). A different preparation of St. John's wort—WS 5572—standardized to 5% hyperforin instead of standardized hypericin was used in another study (Kalb, Trautmann-Sponsel, & Kieser, 2001). In the study by Kalb and colleagues, individuals with mild to moderate depression instead of major depression were included. Another study utilized another formulation of *Hypericum* extract—WS 5570 (600 or 1,200 mg daily dose; 0.12% to 0.28% hypericin, 3% to 6% hyperforin)—for individuals with mild to moderate depression (Kasper, Anghelescu, Szegedi, Dienel, & Kieser, 2006). The study utilizing LI 160 recorded the *Hypericum* preparation as equally effective compared with placebo, while Kalb and colleagues and Kasper and colleagues found *Hypericum* extracts WS 5572 and WS 5570, respectively, to be significantly better than placebo in reducing depression, as measured by the Hamilton Depression Rating Scale (HAM-D) scores. There are many other dissimilar studies that are compared regularly in literature reviews. Meta-analyses reviewing and separating subject populations and medication standardizations are imperative to develop a better understanding of *Hypericum* efficacy.

Side Effects and Drug Interactions. Hyperforin has a high affinity for the pregnane X receptor, which regulates CYP3A4 (cytochrome P450 3A4), an enzyme that helps metabolize many different drugs (Moore et al., 2000). Binding to pregnane X leads to the induction of CYP3A4, which would increase the metabolism and decrease the bioavailability of drugs metabolized by this cytochrome P450 system. Since this drug–herb interaction can potentially result in a decrease in the efficacy of the drugs that use CYP3A4 for metabolism, lists of such pharmaceuticals should be reviewed prior to starting patients on St. John's wort (Henderson, Yue, Bergquist, Gerden, & Arlett, 2002; Ogu & Maxa, 2000). Owing to high variability among study methodologies, meta-analyses were used to identify common side effects. Although side effects are less common for St. John's wort when

compared with conventional antidepressants, photosensitivity appears to be a common adverse effect with this herb, and patients should be advised to stay away from the sun or use sunscreen while taking St. John's wort. Gastrointestinal symptoms have also been reported with St. John's wort and should be monitored (Linde, Berner, & Kriston, 2008; Linde & Knuppel, 2005).

Dosage. St. John's wort's dosing range varies between 500 and 1,200 mg daily, with 900 mg/day being the most commonly used dosage. There are multiple standardizations, but the following formulations are considered the most common: LI 160 (900 mg daily dose; 0.72 to 0.96 mg hypericin/900 mg), WS 5572 (900 mg daily dose, 5% hyperforin content), WS 5570 (900 mg daily dose; 0.12% to 0.28% hypericin, 3% to 6% hyperforin).

Kava or Kava Kava (*Piper methysticum*)

Potential Mechanism of Action. The mechanism of action of kava as an anxiolytic is not completely known. The main active compounds in kava are kavalactones such as kavain, 5,6-dihydrokavain, methysticin, dihydromethysticin, yangonin, and desmethoxyyangonin. These putative active compounds have been reported to influence the central nervous system (CNS) by modulation of ion channels. High sodium influx and ion channel disequilibrium are linked to mood and several mental ailments (Imbrici, Camerino, & Tricarico, 2013). Kavain and methysticin inhibit Na+ channels (Gleitz, Gottner, Ameri, & Peters, 1996; Magura, Kopanitsa, Gleitz, Peters, & Krishtal, 1997) and noradrenaline reuptake (Seitz, Schüle, & Gleitz, 1997), and kavain and dihydromethysticin inhibit Ca+ channels and promote the action of ipsapirone, an endogenous serotonin agonist (Walden, von Wegerer, Winter, Berger, & Grunze, 1997). In addition to modulating ion channels, kava has also been shown to inhibit MAO-B (Uebelhack, Franke, & Schewe, 1998) and modulate GABA receptor binding (Jussofie, Schmiz, & Hiemke, 1994).

Evidence. Kava has been used for sedation in traditional medical practices. The plant appears promising in the management of symptoms associated with anxiety disorders, but the controversy surrounding kava-induced liver toxicity has resulted in a decrease in its use. Studies on the efficacy of Kava are generally small, but the methodology and evidence is consistent. A double-blind placebo-controlled study using WS 1490—a standardized product with 70 mg kavalactones/100 mg—showed that after only 1-week, patients who received this formulation had a significant improvement in their anxiety as measured on the Hamilton Anxiety Scale (HAMA) compared with patients who were on placebo (Lehmann, Kinzler, & Friedemann, 1996). The dosage of kava was three capsules daily—210-mg kavalactones daily—and continued for an additional 3 weeks, with HAMA scores continuing to improve. Another double-blind placebo-controlled study using WS 1490 in climacteric women showed the efficacy of kava in this patient population. This study (Warnecke, 1991) used the same kava dosage as Lehmann and colleagues' study. Again, after only 1 week, there was significant improvement in the HAMA score in the kava group compared with the placebo group. A more recent open study on perimenopausal women using kava also reported positive results with kava. After 1 month, there was a significant decrease in anxiety as measured by the State Trait Anxiety

Inventory (STAI) self-administered evaluation. The dosages of kava in the two groups that were included in this study were 100 and 200 mg daily with 55% kavaina.

In addition to placebo-controlled studies on the use of kava for anxiety, there are reports on the efficacy of kava in treating depression when compared with pharmaceuticals such as opipramol and buspirone (Boerner et al., 2003). In addition, d, l-kavain, a putative active compound in kava, has been reported to be as effective as oxazepam (Lindenberg & Pitule-Schödel, 1990). Kava has also been used to manage symptoms associated with benzodiazepine withdrawal (Malsch & Kieser, 2001).

Based on the current published studies, while there is substantial supportive evidence for the use of kava in the management of anxiety and depression, many of these studies lack the scientific rigor such as adequate duration of the study and/or adequate sample size. The variation in efficacy with kava could also be due to variabilities in gender, age, and GABA-transporter polymorphism (Sarris et al., 2013; Witte, Loew, & Gaus, 2005). These variables should be evaluated in future studies.

Adverse Effects and Drug Interactions. Hepatotoxicity is considered the main serious adverse effect with kava that warrants frequent monitoring with liver function tests. Hepatotoxicity has been reported in over 100 cases worldwide (Li & Ramzan, 2010) and has led to a ban on kava supplements in several countries. Allergic reactions, gastrointestinal complaints, and tachycardia have also been reported with kava.

Regarding hepatotoxicity, an animal study conducted over a long period with a high dosage found no signs of toxicity (Sorrentino, Capasso, & Schmidt, 2006). The exact mechanism for the liver damage is unknown, and it has been attributed to some of the active components of the plant and concurrent consumption of kava with alcohol (Li & Ramzan, 2010). Hepatotoxicity has also been attributed to the use of contaminated and moldy kava, as mycotoxin-producing *Aspergillus* bacteria species have been found in the extract (Teschke, Sarris, & Schweitzer, 2011).

Concomitant use of kava with any hepatotoxic or sedative drug should be avoided to prevent drug–herb interactions. Aside from alcohol, drugs posing a potential additive effect to the sedative properties of kava include pregnane steroids, pentobarbital, and benzodiazepines (Almeida & Grimsley, 1996).

Dosage. The recommended dose of kava is 300 mg daily with 70% or 55% kavalactones, pertaining to 210 and 165 mg kavalactones, respectively. Smaller doses such as 150 mg daily have been used as well.

Rhodiola rosea

Potential Mechanism of Action. It has been reported that *R. rosea* significantly inhibits MAO-A, which breaks down serotonin and norepinephrine (van Diermen et al., 2009). MAO inhibition is purportedly caused by some of the putative active compounds of *R. rosea* such as rosidirin, or a combination of rosidirin, cinnnamyl alcohol, triandrin, EGCG dimer, and rhodioloside (van Diermen et al., 2009). Although a number of active compounds have been suggested to contribute to CNS effects of this herbal extract, rhodioloside and tyrosol are suggested as the primary compounds contributing to the alleviation of symptoms associated with depression (Panossian et al., 2008).

Evidence. Preliminary studies on *R. rosea* in the management of anxiety and depression appear to be promising on the basis of a commonly used anxiety scale, HAMA (Bystritsky, Kerwin, & Feusner, 2008; Darbinyan et al., 2007). Although the sample size was very small in one of the studies (N = 10) and the study was not placebo-controlled, it addressed anxiety directly and the mean HAMA scores were significantly different compared with baseline. The formulation used in this study was Rhodax twice daily. Rhodax contains 170 mg *R. rosea* with 30 mg of each of the following: rosavin, rosarin, salidroside, rosin, rhodalgin, acetylrhodalgin, rosaridin, and rosaridol (Bystritsky et al., 2008). In another study, standard doses of *Rhodiola rosea* at 340 mg/day and 680 mg/day for 6 weeks were sufficient to significantly lower reports of somatization, emotional instability, and insomnia compared with placebo (Darbinyan et al., 2007). *Rhodiola rosea* appears promising as an adjunct therapy in combination with TCAs in treating psychopathological symptoms (Brichenko, Kupriyanova, & Skorokhodova, 1986). Animal studies with a standardized formulation of *R. rosea* (SHR-5, 3% rosavins and 0.8% salidroside) have also resulted in similar or potentially greater efficacy than conventional antidepressants such as fluoxetin (Panossian et al., 2008; Perfumi & Mattioli, 2007).

Side Effects and Drug Interactions. Reported side effects with *R. rosea* are generally mild and rare and include dry mouth and dizziness. At very high doses (>3 g/day), *R. rosea* may cause insomnia (Bystritsky et al., 2008). Multiple studies utilizing the standardized SHR-5 for applications similar to anxiety and depression reported no serious adverse events (Olsson, von Schéele, & Panossian, 2009; Spasov, Wikman, Mandrikov, Mironova, & Neumoin, 2000).

Dosage. The most commonly studied preparation of *R. rosea* extracts is SHR-5, which contains 3% rosavin and 0.8% salidroside (Spasov et al., 2000). There are also studies measuring additional putative compounds of *R. rosea* such as tyrosol and triandrin (Panossian, Hamm, Kadioglu, Wikman, & Efferth, 2013; Panossian, Wikman, Kaur, & Asea, 2012). The doses of SHR-5 in studies range from 100 mg daily to higher doses of 680 mg daily, with an average recommended dose of 360 mg/day (Darbinyan et al., 2007; Spasov et al., 2000).

Conclusion: St. John's Wort, Kava, and *Rhodiola rosea*

Although St. John's wort could be an attractive remedy in treating depression, more studies with uniform methodology are needed to prove its efficacy. In some studies, St. John's wort demonstrated superiority over placebo, while in others no improvement was reported compared with placebo. The metabolic pathway of *Hypericum* extract is CYP3A4, which is used by many other drugs. Caution should be practiced when St. John's wort is taken concomitantly with such drugs to avoid drug–herb interactions. Kava is widely used in treating anxiety disorders and has demonstrated efficacy and relative safety in multiple clinical trials. Since large and long-term studies are scarce, chronic and prolonged use is discouraged. Recent reports on kava-induced hepatotoxicity warrant close monitoring of liver function. Although *R. rosea* appears safe and promising in the management of anxiety and mild depression, additional long-term studies with larger sample sizes are needed to validate the use of this plant.

UTI: Cranberry (*Vaccinium macrocarpon*)

Introduction

UTI is a common medical problem, and it is estimated that 10.8% of women in the United States experience UTI annually, with an estimated one in three women visiting a primary care provider for UTI by age 26 (Foxman, Barlow, D'arcy, Gillespie, & Sobel, 2000). Recurrence can be common for those with a history of UTI, and risk of UTI can vary with age and sexual activity (Hooton et al., 1996). Although antibiotics are recommended to treat UTI, cranberry-based supplements were considered one of the top-selling herbs as adjunct preventive therapy in 2012 with sales over $60 million in the United States (Lindstrom et al., 2013).

Potential Mechanism of Action

Pathogenesis and virulence of UTI is determined by several factors, including bacterial adhesion, hemolysin, serum resistance, and type of capsular polysaccharide (Johnson, 1991). Early studies suggest urine acidification to have a bacteriostatic effect, but the change in pH appears insignificant or unnecessary in the management of UTI (Avorn et al., 1994; Liu, Black, Caron, & Camesano, 2006). The most popular mechanism of interest in UTI prevention is through inhibition of bacterial adhesion of *Escherichia coli* fimbriae. In a study using cranberry juice at 1:2 dilution, type 1 fimbriae, a mannose-sensitive adhesin, was inhibited by fructose, with an *in vitro* recording of almost no yeast aggregation (Zafriri, Ofek, Adar, Pocino, & Sharon, 1989). A more recent *in vitro* study has also determined that type A proanthocyanidins—included within the categories of flavonoids or polyphenols—decrease the mannose-resistant adhesin P-fimbriae in a dose-dependent manner (Gupta et al., 2007). This has been observed at a molecular level, with cranberry juice precipitating conformational change of P-fimbriae *in vitro* (Liu et al., 2006).

Evidence

While there is evidence promoting the use of cranberry for prevention of UTIs, inconsistent methodology leads to conflicting conclusions among studies. In one 2-month ex vivo study, cranberry juice (dried; polyphenolic content 3% m/m) at 1,200 mg/day yielded significantly less adherence by uropathogenic *E. coli* (Valentová et al., 2007). Stothers (2002) and Wing and colleagues (Wing, Rumney, Preslicka, & Chung, 2008) also reported favorable results for cranberry, with 250 and 240 mL of a standardized cranberry juice, in reducing UTI. Wing and colleagues estimated the standardized juice content to have 106 mg of proanthocyanidins. When compared with antibiotics trimethoprim (TMP; 100 mg) and trimethoprim–sulfamethoxole (TMP–SMX; 480 mg) for the management of UTI, cranberry appeared equivalent to TMP and inferior to TMP–SMX (Beerepoot et al. 2011; McMurdo, Argo, Phillips, Daly, & Davey, 2009). On the other hand, larger studies utilizing a 27% cranberry juice—an average of 112 mg proanthocyanidins/8 oz—concluded that the benefit of cranberry was insignificant compared with placebo (Barbosa-Cesnik et al., 2011; Stapleton et al., 2012). The use of different formulations and doses and lack of standardization in cranberry clinical studies pose challenges in interpreting the results of these studies. Proanthocyanidins are considered main active components in the cranberry when it comes to the prevention of UTI. Further studies

considering proanthocyanidin content are needed in order to determine whether cranberry is an effective preventive measure for UTI.

Side Effects and Drug Interactions

Adverse events from continually taking cranberry supplements are few and minor, with many study durations being 6 months to 1 year. Adverse reports include gastrointestinal and vaginal irritation (Stapleton et al., 2012), nocturia (McMurdo et al., 2008; Valentová et al., 2007), sensitive nipples (McMurdo et al., 2008), and stomach acidity (Valentová et al., 2007). Multiple studies reported no serious adverse effects (Beerepoot et al., 2011; Kontiokari et al., 2001) or adverse reactions similar to those reported in the placebo group (Barbosa-Cesnik et al., 2011). Although cranberry studies lacked standardization because they recruited an expansive age range and employed different forms and dosages, cranberry appears to be safe. Two smaller studies administered high concentrations of the active constituents, phenolics (proanthocyanidins)—37% to children and 30% to adult women—and reported no serious adverse events (Afshar, Stothers, & MacNeily, 2012; Bailey, Dalton, Daugherty, & Tempesta, 2007). Cranberry juice can raise the risk for calcium oxalate and uric acid stones (Gettman et al., 2005). Persons with diabetes should also consume cranberry juice with caution because of its sugar content. Individuals taking warfarin should be cautious, as cranberry can potentially modulate the pharmacodynamics of warfarin and result in drug–herb interaction (Mohammed Abdul et al., 2008). CYP3A inhibitors have been identified in cranberry, which may account for the altered warfarin metabolism since warfarin uses CYP3A4 for metabolism (Kim et al., 2011).

Dosage

Different formulations of cranberry such as syrup, extract, and tablet have various bioavailability of proanthocyanidin, the primary active ingredient. In standardized formulations of cranberry, 36 to 72 mg/day is recommended as an effective dose to reduce bacterial adhesion (Howell et al., 2010). A pilot study indicated that a higher dosage of 100 mg/day of proanthocyanidin is also safe over a long period (Bailey et al., 2007).

Conclusion

According to the current literature, the efficacy of cranberry for prevention of UTI appears nonconclusive but safe. Larger studies using consistent methodologies and standardized formulation of cranberry need to be carried out to determine whether this plant is superior to placebo in UTI prevention. The high incidence of recurrent UTIs among women and the rise in antibiotic-resistant UTIs warrant additional well-designed studies with high enough concentrations of proanthocyanidins.

Premenstrual Syndrome: Chasteberry (Vitex agnus-castus)

Introduction

Pre Menstrual Syndrome (PMS) affects approximately 75% of menstruating women (http://www.mayoclinic.org/diseases-conditions/premenstrual-syndrome), and includes a wide array of symptoms, most of which are related to water retention (bloating, breast

tenderness), negative affect (depression, anxiety), food (cravings), and pain (cramps and aches) (He et al., 2009). Up to 8% of women suffer from severe PMS, which may significantly affect their quality of life (Yonkers, O'Brien, & Eriksson, 2008). The broad array of symptoms and symptom severity, coupled with unknown etiologies for most of these symptoms, complicate the pharmacotherapy of PMS. This may draw more consumer attention to an over-the-counter "natural" PMS remedy such as chasteberry, which purportedly addresses multiple symptoms. Recent studies of chasteberry for the management of PMS symptoms positively support this multimodal remedy, even though the exact mechanisms of chasteberry in managing symptoms of PMS remain undetermined.

Potential Mechanism of Action

Etiology of PMS has been linked to several steroid hormones and neurotransmitters, and their relationship to each other in the hypothalamus–pituitary–ovarian axis, and the CNS (Yonkers et al., 2008). Chasteberry's ability to ameliorate symptoms of PMS is likely due to its action on the hypothalamic–pituitary–ovarian axis. It has been shown that dopaminergic diterpenes rotundifuran and 6β,7β-diacetoxy-13-hydroxy-labda-8,14-dien in *V. agnus-castus* influence dopamine D_2 receptors *in vitro* (Meier, Berger, Hoberg, Sticher, & Schaffner, 2000). Since dopamine helps regulate prolactin levels (tuberoinfundibular pathway), the diterpenes could affect breast pain (mastalgia) associated with irregular prolactin levels. However, a clinical open study by Berger and colleagues (Berger, Schaffner, Schrader, Meier, & Brattström, 2000) recorded improvements in PMS symptoms without significant change in the women's physiologic prolactin levels. Dopamine manipulation could also contribute to decreasing the emotional irregularity (mood swings, depression, anxiety) via the mesocortical pathway. The extract has also been noted to bind estrogen receptors via flavonoids, including apigenin and penduletin (Jarry, Spengler, Wuttke, & Christoffel, 2006). *V. agnus-castus* also demonstrates an agonistic effect on the μ-opiate receptor (Webster, Lu, Chen, Farnsworth, & Wang, 2006), which is associated with analgesia and sedation. The evidence supporting chasteberry's influence on multiple receptors complicates the definition of an exact mechanism of action. However, this multireceptor influence lends support to the idea that the herb normalizes a multitude of PMS symptoms.

Evidence

The duration of placebo-controlled studies with chasteberry is generally over three menstrual cycles to assure evaluating the efficacy of chasteberry for various PMS symptoms. In one study of 162 women, chasteberry at 8-, 20-, and 30-mg Ze440 was compared with placebo. Efficacy was determined by scoring of the visual analogue scale (VAS), with attention to irritability, mood alteration, anger, headache, bloating, and breast fullness. With a symptom score reduction ≥50% defining "responders," the 20-mg dose was the most effective, with 81% responders in the 20-mg group. The smaller dose of 8 mg (14% responders) was not significantly better than placebo (11% responders). The larger dose of 30 mg was not significantly better than the 20 mg dose, but it was still significantly better than placebo (Schellenberg, Zimmermann, Drewe, Hoexter, & Zahner, 2012). An older placebo-controlled trial utilizing 20-mg Ze440 was significantly superior to placebo in alleviating irritability, mood alterations, anger, headache, and breast tenderness (Schellenberg, 2001). In spite of these positive results, two other placebo-controlled

studies reported that chasteberry lowered PMS symptoms, but the placebo response was too high to determine that the herb was effective (He et al., 2009; Ma, Lin, Chen, & Wang, 2010). The majority of non–placebo-controlled studies support the use of chasteberry as well. Although non–placebo-controlled studies may not provide us with definite answers, their data may be used to evaluate adverse effects profile of chasteberry (Berger et al., 2000; Loch, Selle, & Boblitz, 2000; Prilepskaya, Ledina, Tagiyeva, & Revazova, 2006). In these studies, different scales such as premenstrual tension syndrome (PMTS) scale, premenstrual syndrome diary (PMSD), VAS, and clinical global impression (CGI) were used to evaluate PMS symptoms. The evidence supporting chasteberry could be more conclusive if studies used the same scales. There are also studies comparing chasteberry to magnesium oxide (Di Pierro, Callegari, Speroni, & Attolico, 2009) and vitamin B_6 (Lauritzen, Reuter, Repges, Böhnert, & Schmidt, 1997). The latter study is sometimes referenced in support of the efficacy of chasteberry, but equivalence to vitamin B_6 is not meaningful as vitamin B_6 is not an established treatment for PMS symptoms.

Side Effects and Drug Interactions

Adverse effects are mild, with reports of nausea, acne and skin irritation/inflammation (Loch et al., 2000; Schellenberg, 2001), gastrointestinal problems (Loch et al., 2000), headaches (He et al., 2009; Schellenberg et al., 2012), erythematous rash, mild hypertension (Schellenberg et al., 2012), and menstrual disorders (Ma et al., 2010). No serious drug interactions have been reported. Since chasteberry can modulate various hormonal levels, women with diseases sensitive to hormone levels (e.g., breast and ovarian cancer) should be cautious. Oral contraceptive use does not appear to influence chasteberry efficacy (Berger et al., 2000), but women using such birth control methods should take caution for potential hormonal influences.

Dosage

A recent comparative dosage study of chasteberry (Ze440 formulation) concluded that an optimal dose (60% ethanol m/m, drug–extract ratio 6 to 12:1, standardized to casticin) was 20 mg daily, which corresponds to 180 mg of crude *V. agnus-castus* (Schellenberg et al., 2012). The dose of 20 mg was effective in an older study by the same authors as well (Schellenberg, 2001). Two other studies supporting chasteberry's use for PMS symptoms used different doses and extractions (BNO 1095), but the placebo responses were too high to determine whether this formulation was optimal (He et al., 2009; Ma et al., 2010).

Conclusion

There is growing evidence that chasteberry is effective in ameliorating multiple symptoms of PMS with few adverse events. Chasteberry appears to be a safe alternative treatment if PMS symptoms are mild or moderate and individuals are not responding to NSAIDs and SSRIs. In a study of women suffering from severe symptoms of PMS, although chasteberry appeared effective, placebo outcomes were also effective (He et al., 2009; Ma et al., 2010). The exact mechanism of action of the herb and the pathophysiology of the PMS symptoms are still unknown. The herb should be further researched in attempts to replicate positive clinical outcomes using consistent scales and standardized formulations.

Menopause: Black Cohosh (*Actaea racemosa* and *Cimicifuga racemosa*)

Introduction

Menopause is an inevitable hormonal transition for women, with characteristic hot flashes, insomnia, mood swings, night sweats, depression, breast pain, and many other symptoms. Until recently, hormone therapy (HT; estrogen, or estrogen + progesterone) was a standard approach to alleviating such symptoms in women. While HT is still used, the Women's Health Initiative (WHI) study created controversy about using HT, as long-term results were coupled with elevated risks of heart disease, stroke, and breast cancer (Rossouw et al., 2002). The findings of the WHI precipitated a decline in HT use (Hersh, Stefanick, & Stafford, 2004) and an increase in the use of popular herbal alternatives that contain isoflavones (phytoestrogens) such as soy-based products and red clover. Although these products are believed to be safe, the use of phytoestrogens could still be controversial in women with a history of hormone-sensitive cancers. Unlike phytoestrogenic products, black cohosh extract (BCE) does not influence systemic estrogenic activity. While some studies vary in methodology, they are mostly supportive of BCE use for treating menopausal symptoms.

Potential Mechanism of Actions

Black cohosh is thought to modulate menopausal symptoms through the activity of triterpene glycosides, but specific mechanisms are unknown. It is believed to act as a selective estrogenic receptor modifier (SERM), but does not influence breast or vaginal cytology. There are no systemic or breast cytology changes, as epithelial cells and estrogenic marker pS2 remained normal in extracellular components of nipple aspirate fluid (NAF) during a 12-week study (Ruhlen et al., 2007). Changes in endometrial thickness were not evident in Liske and colleague's (Liske et al., 2002) study. In another study, osteoblast activity was increased with black cohosh ethanolic extract, a bone-specific alkaline phophatase—a marker for bone formation (Wuttke, Seidlová-Wuttke, & Gorkow, 2003).

Aside from SERM activity, black cohosh may modify serotonin binding. A study on rats found that black cohosh isopropyl extract inhibits binding of [^{3}H]lysergic acid diethylamide to 5-HT$_7$, a 5-HT subtype concerned with thermoregulation (Burdette et al., 2003). The same study also demonstrated possible serotonin receptor agonistic effects, by elevating cAMP levels in 5-HT$_7$ transfected HEK293 cells (Burdette et al., 2003).

Evidence

An isopropanolic BCE demonstrates effective relief of menopausal symptoms in multiple randomized placebo-controlled 3-month studies. The Menopause Rating Scale (MRS) was used, which is a 10-point questionnaire, including somatic pains (muscle and joint pain), psychological symptoms (irritability, nervousness, depression, etc.), hot flashes, sleeping disorders, and urinary and sexual dysfunctions. In one study, the treatment group (40 mg isopropanolic BCE) experienced significant improvement compared with the placebo; all PMS subcategories significantly improved, except for the somatic symptoms (Osmers et al., 2005). A second study demonstrated significant improvement on the MRS as well, with hot flashes showing the greatest improvement (Ross, 2012). A smaller placebo-controlled study found the extract to be significantly better than placebo in respect to "atrophy" symptoms (vaginal dryness, sexual disorders, urinary complaints).

Other subcategories—psychological, somatic, and hot flashes—were "distinctly improved," but not significant compared with placebo (Wuttke et al., 2003).

While not placebo-controlled studies, two additional trials of isopropanolic black cohosh measured its efficacy with the Kupperman Index score (KI; similar scoring method as MRS) and demonstrated significant improvements in menopausal symptoms with black cohosh. In a study consisting of over 1,800 Hungarian women taking 40-mg BCE for 12 weeks, the women reported an average KI decrease of 17.64 points at the end of the study (Vermes, Bánhidy, & Ács, 2005). A smaller study with identical dosage and duration found a 48% average KI score improvement among women (Ruhlen et al., 2007).

A large placebo-controlled study contradicts BCE efficacy found thus far, with no significant difference in vasomotor frequency or intensity when compared with placebo (Newton et al., 2006). The dose of BCE was much higher in this study compared with that in any other studies. Further studies comparing different black cohosh doses are needed.

Side Effects and Drug Interactions

Black cohosh–induced hepatotoxicity has been reported in four cases. A review of these women and their health at initiation of the clinical tests noted that liver complications were evident prior to using black cohosh (Teschke & Schwarzenboeck, 2009). Additional studies monitoring liver enzymes during a 3-month period of BCE (40 mg) reported no hepatotoxicity with black cohosh (Osmers et al., 2005; Ross, 2012). There is also concern regarding women taking BCE who have a history of hormone-sensitive cancers and/or when HT is contraindicated. This concern is based on the fact that BCE may contain isoflavones such as formononetin. In clinical studies where vaginal cytology (endometrial thickness), breast cytology, and systemic estrogen levels were monitored, no abnormal changes were reported (Liske et al., 2002; Ruhlen et al., 2007; Wuttke et al., 2003). Nevertheless, women with compromised liver function or HT contraindication should be cautious, as the mechanism of action for BCE is still unknown. Adverse effects encompass gastrointestinal discomfort (Liske et al., 2002; Osmers et al., 2005; Ross, 2012; Ruhlen et al., 2007; Vermes et al., 2005), joint aches and musculoskeletal disorders (Liske et al., 2002; Osmers et al., 2005; Vermes et al., 2005), headaches, vaginal dryness, fatigue (Ruhlen et al., 2007), breast/nipple tenderness, fatigue, dysphagia (Ruhlen et al., 2007; Vermes et al., 2005), and allergic reactions (Vermes et al., 2005). Some of these symptoms may not be caused by BCE, as many appeared in placebo groups as well and could have been directly related to menopausal symptoms.

Dosage

Black cohosh should be standardized to triterpene glycoside content, usually 2.5%. Doses as high as 200 mg have been tested (Newton et al., 2006), but based on published studies, an effective and commonly tested dose appears to be an isopropanolic extract (Remifemin), 40 mg daily in liquid or tablet form. An aqueous ethanolic extract (58% vol/vol) of 40 mg daily has also been used successfully.

Conclusion

Black cohosh appears to be a promising safe alternative to HT to manage menopausal symptoms. Further studies to establish the effective dose and the exact mechanism of action of the herb should be performed.

Insomnia: Valerian (Valeriana officinalis)

Temporary sleep difficulty can result from factors such as elevated stress and anxiety, consumption of caffeine or alcohol, or changes in sleeping environment. When chronic, it is an insomnia disorder, and can stem from more serious neurological imbalances and medical disorders (Ohayon, 1997). The American Insomnia Survey (AIS) recorded insomnia in over 20% of the national population sample, with greater prevalence among women (Kessler et al., 2011). Those suffering from insomnia can experience a significant decrease in quality of life in addition to further dysfunction, including sequential comorbid depression (Katz & McHorney, 2002; Staner, 2010). Chapter 17 presents detailed information on promoting healthy sleep in women.

Potential Mechanism of Action

An exact mechanism of action of valerian for the management of insomnia is not established. This may be due in part to the variations in composition among valerian species, processing methodology, and environmental population factors (Houghton, 1999). *V. officinalis* is more commonly studied and contains the active constituents valepotriates (monoterpenes), valerinic acid, kessyl glycol, and other sesquiterpenes. These compounds influence GABA pathways, similar to mechanisms of the sedative and anesthetic, pentobarbital and diprivan (Propofal) (Nelson et al., 2002). Valerian elevates GABA levels—as demonstrated *in vitro*—by inhibition of GABA uptake and potentiation of K^+-stimulated GABA release (Ortiz, Nieves-Natal, & Chavez, 1999). Elevated GABA levels may also be due to significant levels of GABA within the herbal extract, but there is conflicting evidence (Ortiz et al., 1999). Lignans within valerian may also contribute to improved sleep, with one study reporting partial agonism of A_1 adenosine receptors (Schumacher et al., 2002).

Evidence

A relatively recent study that was almost double the size of any previous valerian study (N = 434) showed little difference between *Valeriana* (valerian forte 200 mg, 3 tablets before bed; equivalent to 3,600 mg *V. officinalis*) and placebo (Oxman et al., 2007). Sleep diaries were used throughout the study period, taking the tablets before sleeping for 14 days. Even though this study is larger than other published studies on valerian, owing to a number of methodological issues, researchers were not able to draw definitive conclusions. There are single ethanolic, valepotriate, or aqueous herbal extracts, as well as valerian–hops and valerian–lemon balm preparations (Taibi, Landis, Petry, & Vitiello, 2007). In addition, cohorts may be comprised of healthy individuals or those who experience primary, secondary, or comorbid insomnia (Taibi et al., 2007). Inclusion of the secondary and comorbid conditions may be confounding factors in interpreting the efficacy of valerian for the management of insomnia. The most studied *valerian* preparation is ethanolic extract LI 156 (Sedonium). This extract has been compared to benzodiazepines such as oxazepam (Dorn, 2000; Ziegler, Ploch, Miettinen-Baumann, & Collet, 2002), but quality placebo-controlled studies are limited, making it difficult to establish the efficacy of valerian (Bent, Padula, Moore, Patterson, & Mehling, 2006; Taibi et al., 2007).

Side Effects and Drug Interactions

Side effects are generally mild and may include dizziness, headache, diarrhea, gastrointestinal disturbances, and related symptoms (Taibi et al., 2007). The incidence of these side

effects appears to be similar in the placebo group (Oxman et al., 2007). Consumers should be critical in selecting the herb manufacturer, as a recent consumer lab report indicated that a substantial percentage of valerian product labeling is inaccurate and possibly contaminated with lead (http://www.consumerlab.com).

Dosage

The most studied standardized preparation of valerian is LI 156 taken at 300 to 600 mg before sleeping (Taibi et al., 2007).

Conclusion

The efficacy of valerian is uncertain because of the highly variable research methodology across studies. While multiple trials both support and refute valerian for treating insomnia, there is a general consensus that the herb is safe. This may be a viable option for women who respond poorly to benzodiazepines and other sleep medications. Consumers should be cautious of the manufacturing company in view of recent reports of some products being contaminated with lead.

Summary

Herbal remedies have been used in traditional medical practices around the world for thousands of years. When prepared and recommended by indigenous and well-trained practitioners, they appear to be effective. When herbal remedies are used outside their traditional culture, their quality should be scrutinized due to lack of regulation by the FDA. Use of herbal medicine is prevalent in the United States, especially among women. The public perceives herbal remedies as a more natural, safe, and affordable treatment option. Scientifically unfounded statements through social media and advertising, peer community anecdotal evidence, and cultural practices may contribute to this view. As a result, many women embrace herbal therapies without consulting or communicating with their primary care provider. Such practices have the potential to be costly because of potential side effects, toxicity, and drug–herb and drug–disease interactions. Many well-researched herbs are not fully understood mechanistically and may contain heterogeneous and conflicting clinical results in regard to efficacy and safety. If health professionals initiate discussion of herbal medicine use and approach it from an objective and educated standpoint, patients may be more likely to share what herbal remedies they are utilizing. This practice advocates for a more open, safe, and comprehensive approach to care that can potentially lower incidences of acute illness and hospitalization due to herb–drug interactions.

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Women's Health and Wellness Across the Lifespan

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