Herbal and nutritional support for PMS and female menstrual dysfunction

During reproductive years, a staggering number of women experience endocrine disruption via the hypothalamic-pituitary-gonadal axis. Pre-menstrual syndrome (PMS) is amongst the most common presentations, affecting 70-90% of women during their menstruating years.1 PMS is characterised by the cyclic recurrence of physical, mental and cognitive symptoms, typically experienced in the luteal phase of the menstrual cycle after ovulation when progesterone peaks then falls. Premenstrual dysphoric disorder (PMDD) is a severe form of PMS which is incapacitating and affects approximately 5% of women.2

One woman’s PMS is not another’s and clinical presentations vary significantly both in the type and severity of symptoms. Common symptoms and classifications are detailed opposite in figure 1. PMS is commonly seen as a trivial health issue, however for some PMS can have marked impacts on quality of life. In traditional medicine systems, a smooth menstruation is viewed as a sign of health and PMS is viewed as an imbalance which can be corrected.3 Addressing underlying causes may significantly enhance overall health and a sense of wellbeing.

Conventional treatment of PMS includes over-the-counter and prescription medicines; specifically, analgesics, the oral contraceptive pill for hormone control and anti-depressants; with these medications associated with a number of side effects.4, 5

Research has shown that 80% of women with symptoms of PMS self-medicate with OTC products including natural products containing herbs, vitamins and minerals.6

A number of treatment approaches are available to CAM practitioners, each with varying evidence and efficacy. A systematic review identified 205 citations in relation to 62 herbs, vitamins and minerals used in the management of PMS and PMDD. Of these, only 29 articles on 10 ingredients were randomised controlled trials (RCTs) and met the criteria for evaluation. Amongst the ingredients identified to have the greatest evidence were Vitex agnus-castus (Chaste Tree), Coccus sativus (Saffron), vitamin B6, magnesium and calcium.7

Pathophysiology and risk factors of PMS

Understanding of the aetiology of PMS is limited. However, a number of mechanisms involved in the pathophysiology of PMS have been identified, and it is possible that different mechanisms may account for different groups of symptoms.8 Potential mechanisms are summarised in table 2 (back page).

Vitex agnus-castus in PMS

The dried ripe fruit of Vitex agnus-castus (Chaste Tree) has a long history of use in herbal medicine and has been cited by both Hippocrates and Dioscorides for effects on female reproduction. Scientific interest on the herb developed in Germany in the 1930’s, and today a number of clinical studies support the use of Chaste Tree in PMS and other symptoms and conditions specific to women’s health.9 Although the active principles of Chaste Tree have not been conclusively determined, modern analysis has isolated two iridoid glycosides, agnuside and aucubin which may be used as standardisation and quality markers for herbal extracts of Chaste Tree.9

A number of clinical trials have demonstrated the efficacy of Chaste Tree in reducing symptoms of PMS and corpus luteum insufficiency.10-13 A recent systematic review of the effects of acupuncture and herbal medicine in PMS/PMDD analysed four randomised controlled trials (RCTs) on Chaste Tree. In all studies, psychological and physical symptoms of PMS showed more than 50% improvement over control groups.10 A significant reduction in symptoms was reported after 3 months of treatment. Evidence-based doses range from 30mg to 2400mg daily (herbal equivalent from hydroethanolic extracts). This significant dosage variation (compounded by often poorly reported dosages and preparations in the published literature) complicates clinical prescribing of Chaste Tree.10

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Table 1: Abraham’s five PMS ‘types’.

<table>
<thead>
<tr>
<th>PMS-A</th>
<th>PMS-C</th>
<th>PMS-D</th>
<th>PMS-W</th>
<th>PMS-P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>Cravings</td>
<td>Depression</td>
<td>Water</td>
<td>Pain</td>
</tr>
<tr>
<td>Nervous tension, irritability, mood changes, anxiety</td>
<td>Increased appetite, headaches, fatigue, diziness, heart pounding</td>
<td>Depression, forgetfulness, crying, confusion, insomnia</td>
<td>Fluid retention, weight gain, swelling of extremities, breast tenderness, abdominal bloating</td>
<td>Aches and pains, reduced pain threshold</td>
</tr>
</tbody>
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This technical sheet (V10/16) is intended for the further education of practitioners. Any statements made do not intend to claim a cure for any condition mentioned.

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Chaste Tree regulates the hypothalamic-pituitary-gonadal axis. Specifically, it is a potent prolactin inhibitor and dopamine agonist, resulting in secondary progestagenic effects. Prolactin release is regulated by the hypothalamus and dopamine inhibits its release. By binding to dopamine receptors in the anterior pituitary, Chaste Tree prevents the excess production of prolactin. The resulting decrease in prolactin promotes ovulation and allows normal corpus luteum development. This action increases progesterone and prevents symptoms of PMS, as seen in Figure 2 below. This mechanism is also likely to be responsible for the role of Chaste Tree in enhancing female fertility.

Chaste Tree is generally well tolerated and where side effects have been reported, they have generally been minor and transient. Although Chaste Tree is beneficial for spasmodic dysmenorrhea associated with PMS and congestive dysmenorrhea, caution may be required in pure spasmodic dysmenorrhea (due to potential for aggravation via progesterone induced endometrial prostaglandin release). Some practitioners recommend Chaste Tree is avoided for some months following cessation of the oral contraceptive pill to allow restoration of a natural endocrine function.

Figure 2: Chaste Tree promotes a healthy menstrual cycle and reduces symptoms of PMS by reducing prolactin release and increasing progesterone.

Crocus sativus in PMS

*Crocus sativus* (Saffron) is a member of the iridaceae family, and the fine threadlike stigmas of the plant have a long history of use in folk medicine as well as Ayurvedic, Persian, Chinese and American traditional herbal medicine systems. Native to the Middle East and the countries of the Mediterranean, today Spain and Iran provide in excess of 80% of the world’s production. With three stigmas to every flower, approximately 150,000 flowers must be harvested to produce one kilo of dried Saffron and thus it is considered (by weight) to be the most expensive spice in the world. Fortunately, the relatively low therapeutic dose of Saffron extract allows for its use without exorbitant costs to patients. Extracts of Saffron stigma are however at high risk of adulteration and ensuring authentic material is critical for both safety and efficacy.

The stigmas (interestingly the female reproductive organ of the plant) have traditionally been used in menstrual disorders such as menstruation, metrorrhagia, dysmenorrhea, amenorrhea, hardness and adhesions of the uterus as well as mood disorders such as depression and nervousness. Other traditional uses include the relief of general debility, pain, colds, stomach ailments and as an aphrodisiac. In Ayurveda, Saffron is said to support the tonic action of other herbs, particularly those acting on the female reproductive system and nervous system. Saffron has not been widely used in traditional Western herbal medicine, yet usage has increased significantly in recent years; probably due to the publication of a number of clinical studies demonstrating the pharmacological activity and medicinal properties of Saffron, and due to an increasing awareness of the medicinal properties of herbs in various traditional paradigms.

Clinical studies support the use of Saffron in mood conditions and PMS. A double-blind RCT compared the administration of 30mg per day of Saffron (hydroethanolic extract administered as 15mg per capsule twice daily) to placebo in 50 women aged 20 – 45 years. Subjects had regular menstrual cycles and had experienced symptoms of PMS for at least six months prior to the study. Baseline data was gathered over two cycles followed by administration of treatment for a further two cycles. Outcomes measured were the Daily Symptom Report of 17 symptoms as well as the Hamilton Depression Rating Scale (HAM-D scale). 76% of the Saffron group reported a reduction in PMS symptoms of 50% or more compared to 3% of the placebo group (p<0.0001). Furthermore, 60% of the Saffron group reported a positive response (i.e. greater than 50% reduction in symptoms) as measured on the HAM-D scale compared with 4% of the placebo group (p<0.0001). These results are presented in figure 3 opposite.

There is an overlap between the symptoms of PMS and those of depression, and Saffron has been shown to significantly reduce the symptoms of mild...
to moderate depression. A number of high quality, double-blind RCTs have evaluated a concentrated extract of Saffron (30mg daily) in patients with mild to moderate depression. A meta-analysis of 15 RCT's reported Saffron was significantly more effective than placebo and had similar efficacy to that of commonly used antidepressants fluoxetine and imipramine. The beneficial outcome was demonstrated by improvement in the HAM-D scale. Saffron has also been found to significantly improve sexual dysfunction related to fluoxetine treatment in women suffering depression.

Apocarotenoid glycosides crocin, crocetin and picrocrocin and the volatile oil safranal have been identified as primary active components of Saffron. A number of underlying mechanisms of action have been suggested to account for the effects on mood and reproductive health, including:

1. Serotonergic modulation
2. Hypothalamic-pituitary-adrenal-modulating effects
3. Reuptake inhibition of monoamines, dopamine, serotonin and norepinephrine
4. N-methyl-aspartate antagonism
5. Neuroprotective effects, including improved brain-derived neurotrophic factor
6. Antioxidant and anti-inflammatory activity

Magnesium in PMS
Magnesium deficiency and PMS share several similar symptoms, such as anxiety, depression, fatigue, cramping, irritability and headaches. Some studies report lower magnesium dietary intake and significantly lower plasma and erythrocyte magnesium levels in women with PMS compared to controls. Supplementation with 200-400mg of magnesium daily has been shown to improve symptoms of PMS in uncontrolled and double-blinded trials following 2 months of treatment.

One study found that the combination of magnesium (250mg/day) and vitamin B6 (100mg/day) was more effective in reducing symptoms of PMS than either of these nutrients alone.

The therapeutic potential of magnesium in PMS may be due, at least in part, to the functional role of magnesium as a co-factor in cell membrane stabilisation, mitochondrial energy production and progesterone synthesis; and to the role of magnesium in smooth muscle relaxation.

Vitamin B6 in PMS
A high prevalence of vitamin B6 (pyridoxine) deficiency has been reported in women with PMS, and supplementation with pyridoxine has improved both vitamin B6 status and PMS symptoms. Pyridoxine has been subject to a number of uncontrolled and controlled studies in the treatment of PMS. The majority of these trials found that pyridoxine supplementation in doses of 40mg – 500mg daily relieved a number of symptoms associated with PMS. Results were mixed though and methodological limitations were noted in several of the studies. Doses of 200mg or less may be optimal given higher doses for longer periods of time have been reportedly associated with sensory neuropathy.

In one randomised, double-blind crossover trial, 48 women with PMS received 100mg of pyridoxine or placebo for 2 months, followed by the alternative treatment. Pyridoxine supplementation resulted in a significantly greater improvement in PMS symptoms compared to placebo (83% versus 33%; p < 0.001).

Benefits in PMS symptoms following pyridoxine supplementation may result from increased serotonin, dopamine and progesterone levels; improved steroid hormone receptor activity and reduced adverse effects caused by oestrogen excess.

Zinc in PMS
Due to its role in protein manufacture, on a basic biochemical level zinc is a necessary cofactor for hormone and neurotransmitter synthesis and is involved in reproductive health. Furthermore, zinc finger proteins are implicated in the genetic expression of steroid hormone receptors. Zinc is also involved in cellular division, cell membrane stabilisation and antioxidation. Higher rates of zinc deficiency during the luteal phase have been reported in women suffering PMS compared to controls. Animal studies have suggested that zinc supports progesterone production by the corpus luteum via its role in regulating reactive oxygen species. For these reasons, zinc is often used for nutritional support in women with PMS and mood issues.

Selenium and Iodine in PMS
Due to their role in hormone modulation and corpus luteum development, selenium and iodine may be beneficial in supporting female menstruation. Selenium and iodine support healthy thyroid function due to their role in thyroid hormone production and the conversion of T4 to T3. Thyroid hormones are involved in menstruation and reproductive health. Furthermore, subclinical hypothyroidism has been linked to PMS. The following evidence supports the role of healthy thyroid function in PMS and healthy menstruation:

1. Thyroid hormones are involved in ovarian function
2. Thyroid hormones are involved in steroid hormone metabolism
3. T4 supplementation has been reported in limited research to result in complete resolution of PMS symptoms in many affected women
4. Thyroid hormones are involved in progesterone production. Blood samples collected from a small cohort of women during the luteal phase of the
Table 2: Potential underlying mechanisms involved in the pathogenesis of PMS and related CAMs.

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Supporting evidence</th>
<th>Related CAM</th>
</tr>
</thead>
</table>
| **Serotonergic neuroendocrine dysfunction** | Enhanced sensitivity to normal hormone fluctuations may exist in women with underlying serotonin or dopamine deficiency and inflammation, resulting in PMS symptoms.9 Sex hormones affect neurotransmitters and changes in gonadal steroids that occur during the luteal phase appear to be amplified in women with serotonergic dysregulation. A strong genetic link has been identified.24,44 Serotonin receptor concentration varies with cyclic changes in oestrogen and progesterone levels. Animal studies have found PMS is associated with lower blood concentrations of serotonin, leading to low moods, depression and sleep and appetite disturbances.50 Women with PMS/PFMD have been reported to have lower density of serotonin transport receptors than controls.16 Abnormalities in hormone and neurotransmitter receptor sensitivity and reactivity have been identified in women with PFMD.57 | Saffron                                   
Chaste Tree                              
Vitamin B6                               
Magnesium                                
Zinc                                     
Selenium                                 |
| **Inability to convert linoleic acid (LA) to prostaglandin** | A 1984 study found significantly elevated levels of phospholipids LA in women with PMS, whereas concentrations of all metabolites were significantly reduced. The inability of women with PMS to convert LA to gamma-linolenic acid (GLA) results in increased sensitivity to luteal phase steroid hormones and prolactin.16 | Chaste Tree                              
GLA/Evening                              
Prenatal Oil                              |
| **Oestrogen excess or deficiency**     | Oestrogen deficiency is associated with luteal insomia & depression, whereas sufficient oestrogen is linked to positive mood and wellbeing. This is likely to be due to the serotonergic action, and MDD inhibiting effects of oestrogen.60-62 Preliminary genetic findings suggest an association between impaired oestrogen receptor sensitivity and metabolism and dopamine levels in the brain.63 Oestrogen excess is associated with irritability, breast tenderness, fluid retention and suppressed thyroid function. It may also result in excess histamine and related symptoms; specifically, headaches, anxiety, insomnia, brain fog. | Saffron                                   
Vitamin B6                               
Zinc                                     
Iodine                                   
Selenium                                 |

A number of risk factors may increase women's susceptibility to PMS, including:

- Stress
- Body mass index (BMI) >27
- Sedentary lifestyle
- High sugar diet
- High caffeine consumption
- Moderate alcohol consumption
- Vitamin, mineral and essential fatty acid deficiencies

Menstrual cycle showed that deficiency in thyroid hormone level is related to a decrease in progesterone secretion.

5. Selenium supplementation (maintenance dose) has been shown to significantly increase plasma progesterone concentration and support corpus luteum development in animal models.

Adequate iodine intake is important for breast health. Some evidence shows a protective effect of iodine against breast cancer and supplementation with high doses has been shown to relieve symptoms of fibrocystic breast disease and cyclic mastalgia. Additionally, iodine has a down-regulatory effect on oestrogen receptors.64

Other presentations of menstrual dysfunction and selected herbal and nutritional support

In addition to PMS, a number of other menstrual irregularities can present in women. A selection of these are presented in table 3 below. These presentations may also benefit from herbal and nutritional support, including Chaste Tree, Saffron and key nutrients such as magnesium, zinc and vitamin B6.

Table 3: Selected menstrual irregularities and potential herbal and nutritional support.

<table>
<thead>
<tr>
<th>Condition/symptom</th>
<th>Potential herbal and nutritional support</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infertility</td>
<td>Chaste Tree5,15</td>
</tr>
<tr>
<td></td>
<td>Pyridoxine30,32</td>
</tr>
<tr>
<td></td>
<td>Zinc35,42</td>
</tr>
<tr>
<td>Perimenopause and relief of menopausal symptoms such as hot flushes</td>
<td>Chaste Tree6,15</td>
</tr>
<tr>
<td>Amenorrhoea, menorrhagia, oligomenorrhoea and other menstrual cycle irregularities</td>
<td>Chaste Tree6,15</td>
</tr>
<tr>
<td></td>
<td>Saffron12,27,33</td>
</tr>
<tr>
<td></td>
<td>Pyridoxine30,32</td>
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<tr>
<td></td>
<td>Magnesium38</td>
</tr>
<tr>
<td></td>
<td>Zinc35,42</td>
</tr>
<tr>
<td>Benign ovarian and uterine growths</td>
<td>Saffron12,27,33</td>
</tr>
<tr>
<td>Mastalgia</td>
<td>Chaste Tree6,15</td>
</tr>
<tr>
<td></td>
<td>Iodine and selenium35</td>
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</tbody>
</table>

Full reference list available upon request.

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