Trifolium pratense L.

Fabaceae

SCN: red clover, **Part:** flower, herb

QUICK REFERENCE SUMMARY

Safety Class: 1
Interaction Class: A

CONTRAINDICATIONS
None known.

OTHER PRECAUTIONS
None known.

DRUG AND SUPPLEMENT INTERACTIONS
None known.

EDITORS' NOTES
Red clover herb and flower contain approximately 0.17% isoflavones (DerMarderosian and Beutler 2005), with the herb generally containing a higher percent isoflavone content than the flower (Booth et al. 2006). Commercially available red clover products include products with this normal percentage of isoflavones and those modified to contain up to 100% isoflavones. Products with modified concentrations of selected compounds may be expected to have different physiological effects than traditional preparations of the herb. Information on both red clover and red clover derived isoflavones is provided in this entry.

ADVERSE EVENTS AND SIDE EFFECTS
Adverse events reported in clinical trials of red clover products were minor and similar in the placebo and red clover groups (Coon et al. 2007; Lethaby et al. 2007; Low Dog 2005; Nelson et al. 2006).

PHARMACOLOGICAL CONSIDERATIONS
Red clover is commonly cited as a potential anticoagulant due to the presence of coumarins and confusion between coumarins and the anticoagulant drug coumadin (sometimes referred to as coumarin) (Abebe 2002; Booth et al. 2004; Fugh-Berman and Kronenberg 2001; Heck et al. 2000). However, a screening of red clover for 17

Red clover contains isoflavones, compounds that are structurally similar to the human hormone estradiol and capable of binding to estrogen receptors (Umland et al. 2000). Some studies have indicated that red clover isoflavones have a greater affinity for the estrogen receptor β (found primarily in bone, brain, heart, and vascular system) than estrogen receptor α (found primarily in uterus, breast, ovaries, and adrenal glands) (Beck et al. 2005; Dornstauder et al. 2001).
In human studies, conflicting data on the estrogenic activity of red clover have been reported. Some studies have shown no effect on endometrial thickness or vaginal cytology, indicating a lack of estrogenic activity (Baber et al. 1999; Clifton-Bligh et al. 2001; Powles et al. 2008), whereas others showed a decrease in (Imhof et al. 2006) or no effect on (Hale et al. 2001) endometrial thickness or a significant improvement in vaginal cytology (Hidalgo et al. 2005).

PREGNANCY AND LACTATION
Limited information on the safety of red clover in pregnancy or lactation was identified in the scientific and traditional literature. Although this review did not identify any concerns for use while pregnant or nursing, safety has not been conclusively established.

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naturally occurring coumarins identified 5 coumarin compounds in red clover, 1 with anticoagulant activity, 1 with procoagulant activity, and 3 with no activity reported (Booth et al. 2004). No changes in bleeding or blood clotting were observed in women after 30 days of red clover supplementation (Booth et al. 2004).

REVIEW DETAILS

I. Drug and Supplement Interactions

Clinical Trials of Drug or Supplement Interactions

No clinical trials of drug or supplement interactions were identified.

Case Reports of Suspected Drug or Supplement Interactions

No case reports of suspected drug or supplement interactions were identified.

Animal Trials of Drug or Supplement Interactions

No animal trials of drug or supplement interactions were identified.

II. Adverse Events

Adverse Events Reported in Clinical Trials

In a meta-analysis of clinical trials of monopreparations containing red clover isoflavones, the reviewers noted that there was no apparent evidence of adverse events during short-term use of red clover, but long-term studies were lacking. Doses of products in the meta-analysis ranged from 40 to 82 mg daily (Coon et al. 2007).

A second meta-analysis, including six placebo-controlled red clover isoflavone trials, with doses ranging from 40 to 80 mg daily, and study duration from 12 to 16 weeks, concluded that adverse events did not differ between isoflavone and placebo groups, although the events were not well characterized in several trials. Gastrointestinal symptoms were generally the most common adverse events in both isoflavone and placebo groups (Nelson et al. 2006).

A systematic review of phytoestrogens for vasomotor menopausal symptoms, including seven studies on red clover-derived isoflavone extracts, concluded that phytoestrogen products do not appear to have an estrogen agonistic effect on the endometrium when given for up to 1 year. The authors noted that the long-term endometrial safety of high doses of phytoestrogen supplements has not been fully established (Lethaby et al. 2007). Similarly, a review of red clover clinical trials indicated that no adverse effects have been reported, but that the question of safety in hormone-sensitive tissue is important, especially when considering high doses over long periods of time (Low Dog 2005).

Case Reports of Adverse Events

No case reports of adverse reactions were identified.

III. Pharmacology and Pharmacokinetics

Human Pharmacological Studies

No increase in mammographic breast density and no significant effects were observed on estradiol, follicle-stimulating hormone, or luteinizing hormone levels in a trial of women, ages 49 to 65, taking 44 mg red clover-derived isoflavones daily for 1 year (Atkinson et al. 2004).

No significant differences in vaginal cytology, endometrial thickness, serum estradiol, follicle-stimulating hormone, or sex hormone-binding globulin were observed after administration of 40 mg daily of a red clover-based isoflavone extract (Baber et al. 1999). No increase in endometrial thickness was observed after administration of doses up to 85.5 mg daily of a red clover isoflavone preparation for 6 months (Clifton-Bligh et al. 2001). A decrease in endometrial thickness and increase in plasma testosterone levels were observed in postmenopausal women after administration of 80 mg red clover-derived isoflavones daily for 90 days (Imhof et al. 2006). After administration of 50 g daily of a red clover-derived isoflavone extract to perimenopausal women for 3 months, no evidence of an antiproliferative effect in the Ki-67 proliferative marker of endometrial biopsies was found (Hale et al. 2001). In postmenopausal women administered 80 mg daily of a red clover isoflavone supplement for 90 days, significant improvement in all vaginal cytology indices (karyopyknotic index, cornification index, maturation index), as compared to placebo, was observed (Hidalgo et al. 2005).

In women aged 35 to 70 with at least one first-degree relative with breast cancer, administration of 40 mg of red clover isoflavones daily for 3 years did not result in any significant differences in breast density, endometrial thickness, serum cholesterol, follicle-stimulating hormone levels, or bone mineral density, as compared to placebo. In postmenopausal women, some differences in bone marker levels were seen between active and placebo groups at 6 and 12 months (Powles et al. 2008).

In a noncontrolled clinical study of postmenopausal women administered 80 mg daily of red clover-derived isoflavone extract for 6 months, some changes in endometrial activity but no changes in endometrial thickness were observed. Of the 32 study participants, 6 presented with vaginal bleeding and 3 presented with endometrial alteration as compared to the initial exams, 2 developed endometrial cell proliferation, and 1 developed endometrial hyperplasia (Wolff et al. 2006).

A review of studies on red clover and soy-derived isoflavones concluded that 2 mg/kg was a safe daily dose of isoflavones for most populations (Barnes 2003). A second review of studies on red clover and soy-derived isoflavones indicated that 40–50 mg of isoflavones is recommended as the daily dose. This recommendation was based on the daily intake of isoflavones in a traditional Japanese diet (Beck et al. 2005).

No change in prothrombin time or INR time was found after administration of 400 mg daily of red clover extract to postmenopausal women for 30 days (Booth et al. 2004).

Animal Pharmacological Studies

In ovariectomized rats administered 250, 500, or 750 mg daily of a red clover extract (15% isoflavones) for 21 days, a dose-dependent increase in uterine weight and differentiated vaginal cells were observed at the two higher doses, but no stimulation of cell proliferation was observed in the mammary glands. Neither antiestrogenic nor additive estrogenic properties were observed in any of the tissues studied (Burdette et al. 2002).

In ovariectomized rats administered 20 or 40 mg daily of red clover-derived total isoflavones for 14 weeks, treatment with isoflavones significantly increased bone mineral content, mechanical strength of the tibia, femoral weight, and femoral density and prevented the rise of serum alkaline phosphatase levels. In addition, the treatment with isoflavones significantly reduced the number of osteoclasts compared with the ovariectomized control rats (Occhiuto et al. 2007).

In Vitro Pharmacological Studies

In vitro assays of red clover extracts in endometrial cells and MCF-7 (estrogen receptor-positive) breast cancer cells, differential estrogenic activity was observed in the endometrial cells, whereas nondifferential activity was observed in the MCF-7

cells, indicating the significance of the type of bioassay used to determine the estrogenic activity of red clover (Booth et al. 2006).

An extract of a red clover isoflavone preparation increased MCF-7 breast cancer cell proliferation rates (Bodinet and Freudenstein 2004). A standardized red clover isoflavone extract (9% isoflavones by dry weight) showed an affinity for both estrogen receptor (ER) α and β with a significantly stronger affinity for the ERβ receptor in a yeast two-plasmid system (Dornstauder et al. 2001).

A red clover-derived extract of 30% isoflavone aglycones was shown to bind to mu- and delta-opiate receptors in Chinese hamster ovaries (Nissan et al. 2007).

An ethanolic extract of a commercial red clover preparation inhibited the drug-metabolizing isoenzyme CYP3A4 in a fluorometric microtiter plate assay (Budzinski et al. 2000). Genistein and daidzein, metabolites of the predominant red clover isoflavones biochanin A and formononetin, were shown to inhibit the enzyme CYP1B1 (Roberts et al. 2004).

IV. Pregnancy and Lactation

In a study of amniotic fluid samples in women between weeks 15 and 23 of pregnancy, isoflavonoids were detected in 92% of samples. The isoflavonoids daidzein, genistein, formononetin, biochanin A, and coumestrol were detected (Foster et al. 2002).

No information was identified on the safety of red clover use during lactation.

V. Toxicity Studies

Short-Term Toxicity

In ovariectomized sheep, feeding with 3.5 kg daily of red clover silage for 14 days as the sole source of food (81–95 mg/kg daily total phytoestrogens) resulted in increased plasma concentrations of T_3 and T_4 and increased thyroid follicle size as compared to sheep fed hay (Madej et al. 2002).

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