



Red clover (*Trifolium pratense*)

Abstract and key points

Red clover (*Trifolium pratense*) is a medicinal herb containing flavonoids, coumarins, coumestans, and isoflavones that can be taken orally or applied topically. Red clover has been claimed to be effective for the treatment of hot flashes, osteoporosis, and cardiovascular disease. In oncology, it has been claimed to be effective for treating hormonally driven cancers and for reducing hot flashes in women who experience premature menopause as part of their cancer treatment.

The current evidence for its use in women with breast and ovarian cancers based on one systematic review and one additional trial is insufficient.

Evidence is lacking for the use of red clover in women with cancer experiencing hot flashes, and the majority of clinical trials conducted among women without cancer have found that red clover is no more effective than placebo in reducing hot flashes. A single observational study among breast cancer survivors found that women using red clover supplements were less likely to report night sweats.

Preliminary studies suggest that red clover isoflavones may be of benefit in prostate and colon cancers but the evidence is not sufficient.

Although red clover is generally well tolerated by women without cancer, drug-nutrient and nutrient-nutrient interactions are theoretically possible. Safety data is lacking in women with cancer.

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- Red clover (*Trifolium pratense*) is a medicinal herb containing flavonoids, coumarins, coumestans, and isoflavones.
- Red clover has been claimed to be effective for treating hormonally driven cancers and for reducing hot flashes in women who experience premature menopause as part of their cancer treatment.
- The current evidence for its use in women with breast and ovarian cancers is insufficient.
- Safety data in women with cancer is lacking. Generally red clover appears safe to use in women without cancer but theoretically herb-drug and herb-herb interactions are possible.

What is it?

Description

Red clover is a legume in the *Fabaceae* family that is indigenous to Europe and parts of the Middle East and has been naturalized to North America¹.

Scientific Names/Brand Names

Trifolium pratense. Red clover products include Promensil®, Rimostil®, Menoflavon®, and Estrofactors®.

Ingredients

Red clover contains flavonoids, coumarins², isoflavones and is especially high in coumestans. Red clover contains at least 9 isoflavones³ including formononetin and biochanin A (glycosides), and daidzein and genistein (aglycones)¹.

Application and dosage

Red clover is most commonly taken orally but can also be used topically. The recommended daily dose of red clover extracts ranges from 40 to 80 mg daily⁴.

History

For centuries, red clover has been grown in pastures to feed cattle and other grazing animals. Humans have rarely consumed red clover in their diets, although it has a long history of medicinal uses.

Claims of efficacy/alleged indications

Traditionally, red clover has been used for a variety of health conditions. Currently, it is commonly used in the treatment of hot flashes, osteoporosis, and cardiovascular disease. In oncology, it has been claimed to be effective for treating hormonally driven cancers (breast, ovarian, uterine) and for reducing hot flashes in women who experience premature menopause as part of their cancer treatment⁵. Topically, red clover is used for cancer, burns, and chronic skin diseases including eczema and psoriasis.

Mechanism of action

Red clover has been shown to function as both an oestrogen receptor agonist¹ and antagonist, depending on the state of its metabolites ³⁶. Red clover metabolites exhibit a highest affinity for beta-estrogens receptors

yet weak binding affinity for androgen and progesterone receptors⁶. Its anti-neoplastic effects may be attributed to effects on the cell cycle and apoptosis⁷ and COX-⁸ and angiogenesis inhibition⁹.

Prevalence of use

Increasingly, many women are turning to phytoestrogens as an alternative to hormone replacement therapies because of their adverse effects. Precise prevalence figures are unavailable; however, one study reported that 39.5% of 767 breast cancer survivors were using estrogenic botanical supplements¹⁰.

Legal issues

Red clover is sold as a natural health product or herbal dietary supplement in North America and Europe.

Cost and expenditure

An average daily cost of the red clover supplements such as Promensil is €0.70, US\$ 1.00 and CDN \$1.25.

Does it work?

Based on the current available evidence, red clover's efficacy in the treatment of breast, uterine, colon, and prostate cancers is uncertain.

Breast cancer

A meta-analysis of 8 RCTs, including 1287 breast cancer survivors, suggested that isoflavones had no significant effect on breast density among post-menopausal women but there may be a small increase in breast density among pre-menopausal women. The data did not evaluate the effects of red clover alone, but the authors conclude that the available evidence suggests that there is no differential effect based on isoflavone source¹¹. There is a moderate risk of bias in the studies included and the data was deemed insufficient to directly assess the effects of isoflavones on breast cancer or mortality.

The HEAL prospective study conducted among 767 breast cancer survivors found that women using red clover supplements were less likely to report night sweats but there was no effect on hot flushes or quality of life¹⁰. The generalisability of this trial is limited as it included only 38 red clover users.

No additional clinical trials were identified that directly evaluate the effects of red clover isoflavone supplementation in women with breast cancer. One clinical trial among women with an increased risk of breast cancer found that one year of red clover supplementation had no effect on steroid hormone levels compared with placebo¹⁵. Red clover's protective effects in cancer prevention have not yet been demonstrated in clinical studies.

Hot flushes

There are no meta-analyses or controlled clinical trials of the effects of red clover on hot flushes in women with cancer. However, three meta-analyses and systematic reviews have been conducted in women without cancer. Two found that red clover is no more effective than placebo in reducing hot flush frequency [12,13](#) while another reported evidence of a marginally significant effect of red clover on hot flush frequency in menopausal women [14](#). Due to the heterogeneity and limited number of studies included, it is unclear whether the effect is clinical significant.

Uterine cancer

Three clinical trials examined the effects of red clover supplementation on the development of uterine cancer. Red clover supplementation did not affect the proliferative index of endometrial biopsies [16](#), endometrial thickness [17](#), or breakthrough bleeding compared with placebo [18](#).

Colorectal cancer

A 2-month crossover RCT using 84 mg of red clover daily was conducted among 37 men at high risk for colorectal cancer. It found that red clover isoflavone supplementation did not influence serum insulin-like growth factor (IGF-1). However, decreased total IGF-1 concentrations were associated with increased serum equol concentrations, suggesting that isoflavones may lower IGF-1 only among equol producers [19](#).

Prostate cancer

A case-controlled study among 38 men with prostate cancer who received 160 mg of red clover isoflavones found an increase in apoptosis in regions of low- to moderate-grade cancer but no differences in PSA, Gleason score, and serum testosterone [20](#). A case report of a 66 year old male with high-grade adenocarcinoma who, of his own initiative, took 160 mg of red clover phytoestrogens (Promensil) daily for the 7 days leading up to his prostatectomy also reported that his prostatectomy specimen revealed histological changes consistent with tumour regression [21](#).

Pre-clinical studies

Animal and in-vitro studies indicate that red clover isoflavones exert their action by activating both estrogen [22](#) and progesterone receptors [23](#). Results of pre-clinical studies are mixed as red clover has been found to both activate [17](#) and inhibit [24,25](#) the proliferation of breast cancer cells. Preliminary results suggest that it may also inhibit endometrial [24](#) and prostate [26](#) cancer cells. Red clover's anti-neoplastic properties are believed to result from protection against DNA damage [22,23](#), cytotoxic effects, inducing apoptosis [27](#), inhibiting aromatase [28](#), and modulating steroid hormone levels [29-32](#).

It has been suggested that the seasonal variation of red clover isoflavones may in part be responsible for the conflicting findings about red clover's effects [33](#).

Is it safe?

Safety data in women with cancer is generally lacking; the information below refers to women without cancer.

Adverse events

Red clover is generally well tolerated but has been reported to cause minor adverse effects, some occurring at doses as low as 40 mg per day. Adverse effects include: headaches, myalgia, arthralgia, nausea, and diarrhoea², breast tenderness, swollen neck glands, dizziness, vertigo, tremor, hypertension, acne, rash, pruritis, psoriasis, bloating, constipation, mouth ulcer, sore throat, osteoarthritis, bronchitis, low platelets, reflux, epistaxis, menstrual bleeding, urinary tract infection, and vaginal thrush. Compounds and mechanisms responsible for triggering adverse events are currently unknown³³. A large trial of a red clover extract (Promensil) versus placebo reported no differences in the proportion of women who experienced any adverse events and no differences in the rate of specific adverse events between groups³³.

Interactions

There are no reports of clinically significant drug interactions with red clover in the published literature. Red clover isoflavones can inhibit CYP IA1, CYP IBI and CYP 2C9 metabolic liver enzymes and may increase plasma levels of drugs metabolised through these pathways³⁴.

Use of red clover concomitantly with herbs that have constituents that might affect platelet aggregation could theoretically increase the risk of bleeding in some people. These herbs include angelica, clove, danshen, garlic, ginger, ginkgo, *Panax ginseng*, horse chestnut, turmeric, and others⁵.

Use of red clover with oestrogenic herbs and drugs, including tamoxifen, are theoretically contraindicated as red clover may have additive or antagonistic effects⁵.

Contraindications

Some suggest testing prothrombin time and/or partial thromboplastin time prior to initiating therapy³⁴ and avoiding its use in those with bleeding disorders². Individuals with thyroid conditions should use caution when consuming phytoestrogens as one animal study reported higher concentrations of some thyroid hormones with red clover use¹. Red clover is contraindicated during pregnancy³³.

Contamination issues

There are some concerns about the potential presence of coumarins in some products or specific species of red clover which can affect bleeding time. It is therefore contraindicated in those with bleeding disorders.

Citation

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