



This monograph was prepared by The Ottawa Integrative Cancer Centre (OICC), in collaboration with the Complementary Medicine Education and Outcomes (CAMEO) Research Program. It is part of a series of monographs being developed to share results of a review of the research evidence related to common therapies and products used within cancer patient care.

The following monograph is designed to summarize evidence-based research and does not advocate for or against the use of a particular therapy. Every effort is made to ensure the information included in this monograph is accurate at the time it is published.

Please note that this monograph does not include an exhaustive list of all potential adverse events; individuals may experience unique side effects. The information in this monograph should not be interpreted as medical advice nor should it replace the advice of a licensed health care provider. Prior to using a new therapy or product, always consult a licensed health care provider.

For the safe use of natural health products, please consider the following:

- Consult a licensed health care provider prior to using a natural health product and make a plan to monitor its effectiveness and any side effects. This is particularly important for pregnant or breast-feeding women and people with serious medical conditions.
 - To help prevent interactions with your prescribed medication, ensure your health care provider is aware of any drugs or natural health products you may be using. Make sure to note all natural health ingredients listed in compound products.
 - Read and follow all instructions on the product label.
- If purchasing natural health products in Canada, look for Health Canada approved products. Look for Natural Product Number (NPN) or Homeopathic Medicine Number (DIN-HM) on the label to identify licensed products. Avoid internet pharmacies, as the quality of products cannot be guaranteed and products might not be licensed for sale through Health Canada. For more information, visit <http://www.hc-sc.gc.ca/dhp-mpps/prodnatur/about-apropos/cons-eng.php>

Please note: While the aim was to draw from the most extensive research, in some circumstances the information used was limited by the selection and caliber of available research studies. Full references are available in the corresponding full-length monographs found on the CAMEO website.

Disclaimer

The OICC, in collaboration with the CAMEO Research Program, has prepared this monograph, as part of a series of monograph development, to share results of a review of the research evidence related to common therapies and products used within cancer patient care. The following monograph is designed to provide evidence-based research and neither advocates for or against the use of a particular therapy. Every effort is made to ensure the information included in this monograph is accurate at the time it is published. Prior to using a new therapy or product, always consult a licensed health care provider. The information in this monograph should not be interpreted as medical advice nor should it replace the advice of a qualified health care provider.



RED CLOVER

Proper Name

Trifolium pratense

Common Name

Red clover, wild clover

Proprietary Extracts

Promensil; Trinoven, Rimostil

Common Uses in Cancer Care

Treatment of hot flashes

Route of Administration

Oral

Mechanism of Action

Possible selective estrogen receptor modulating (SERM) activity

Clinical Evidence related to Effectiveness

Based on 1 RCT, there is insufficient evidence demonstrating efficacy of red clover in the treatment of hot flashes among breast cancer patients(1). One observational study found that use of red clover supplements was associated with an approximate 60% reduction in the incidence of several menopause-related symptoms including weight gain, night sweats, and difficulty concentrating; however this was based on a small number of subjects utilizing red clover (38 out of 788)(2).

Clinical Evidence related to Risk of Breast Cancer

Based on 2 RCTs investigating various surrogate markers of breast cancer risk and effect on estrogen responsive target tissues, red clover does not appear likely to increase risk of breast cancer among women at high risk of breast cancer based on family history or Wolfe breast density pattern. One RCT showed no effect from red clover supplementation 40mg isoflavones daily on mammographic density, circulating estradiol, LH, or FSH, or tyrosine kinase activity (1). Another RCT found no effect on mammographic density or endometrial thickness (3).

Clinical Evidence related to Estrogenic Effects

Red clover does not have estrogenic effects based on two studies in women at elevated risk of breast cancer (1, 3), and three studies in healthy women (4-6). These studies show no effect from red clover on circulating levels of estradiol, luteinizing hormone (LH), follicle stimulating hormone (FSH), or the

thickness of the endometrial lining of the uterus, which typically increases in response to estrogen (1, 3-6).

Adverse Events and Side Effects

Adverse events were not reported by Atkinson. Powles reported skin related symptoms that were not detailed but were equally distributed between the red clover and placebo groups.

Interactions with other Therapies, including Drugs and Natural Health Products

There is no human level data describing potential interactions between red clover and hormonal therapies such as tamoxifen or aromatase inhibitors. Since red clover and soy contain similar isoflavone profiles, some information may be extrapolated from studies of soy isoflavones alongside tamoxifen and aromatase inhibitors. These studies suggest the possibility of enhanced survival and reduced recurrence in patients using soy alongside tamoxifen and aromatase inhibitors (4-6).

Animal evidence is mixed, with one study showing that extremely high doses of biochanin A, a red clover isoflavone, at 100mg/kg decreased levels of 4-hydroxytamoxifen, the active metabolite of tamoxifen (7). Another animal study showed no effect (8). The applicability of such a dosage level to the much lower dosages consumed by humans is not clear.

In theory, coumarins in red clover may potentiate the effect of antiplatelet medications and should not be used in conjunction with antiplatelet therapy; however this remains a theoretical interaction and has not been demonstrated in humans, including in single case reports. There has been one case reported of a woman taking a combination of red clover, dong quai, ginseng and other herbs, but no prescription medications, developing a spontaneous subarachnoid haemorrhage (9).

Cautions and Contraindications

Antiplatelet medications: use only as recommended by your health care provider.

Contraindicated with surgery; discontinue at least 2 weeks prior to and 2 weeks following surgery.

Dosing, frequency and length of treatment

40mg red clover isoflavones; may be used long term

Disclaimer

The OICC, in collaboration with the CAMEO Research Program, has prepared this monograph, as part of a series of monograph development, to share results of a review of the research evidence related to common therapies and products used within cancer patient care. The following monograph is designed to provide evidence-based research and neither advocates for or against the use of a particular therapy. Every effort is made to ensure the information included in this monograph is accurate at the time it is published. Prior to using a new therapy or product, always consult a licensed health care provider. The information in this monograph should not be interpreted as medical advice nor should it replace the advice of a qualified health care provider.

References (An asterisk (*) denotes open-access articles)

- *1. Atkinson C, Warren RM, Sala E, Dowsett M, Dunning AM, Healey CS, et al. Red-clover-derived isoflavones and mammographic breast density: a double-blind, randomized, placebo-controlled trial [ISRCTN42940165]. *Breast Cancer Research*. 2004;6(3):R170-R9.
 - *2. Ma H, Sullivan-Halley J, Smith AW, Neuhaus ML, Alfano CM, Meeske K, et al. Estrogenic botanical supplements, health-related quality of life, fatigue, and hormone-related symptoms in breast cancer survivors: a HEAL study report. *BMC complementary and alternative medicine*. 2011;11:109. PubMed PMID: 22067368. Pubmed Central PMCID: 3234199.
 3. Powles TJ, Howell A, Evans DG, McCloskey EV, Ashley S, Greenhalgh R, et al. Red clover isoflavones are safe and well tolerated in women with a family history of breast cancer. *Menopause Int*. 2008;14(1):6-12.
 - *4. Kang X, Zhang Q, Wang S, Huang X, Jin S. Effect of soy isoflavones on breast cancer recurrence and death for patients receiving adjuvant endocrine therapy. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*. 2010 Nov 23;182(17):1857-62. PubMed PMID: 20956506. Pubmed Central PMCID: 2988534.
 - *5. Guha N, Kwan ML, Quesenberry CP, Jr., Weltzien EK, Castillo AL, Caan BJ. Soy isoflavones and risk of cancer recurrence in a cohort of breast cancer survivors: the Life After Cancer Epidemiology study. *Breast cancer research and treatment*. 2009 Nov;118(2):395-405. PubMed PMID: 19221874. Pubmed Central PMCID: 3470874.
 - *6. Shu XO, Zheng Y, Cai H, Gu K, Chen Z, Zheng W, et al. Soy food intake and breast cancer survival. *JAMA : the journal of the American Medical Association*. 2009 Dec 9;302(22):2437-43. PubMed PMID: 19996398. Pubmed Central PMCID: 2874068.
 7. Singh SP, Wahajuddin, Raju KS, Ali MM, Kohli K, Jain GK. Reduced bioavailability of tamoxifen and its metabolite 4-hydroxytamoxifen after oral administration with biochanin A (an isoflavone) in rats. *Phytotherapy research : PTR*. 2012 Feb;26(2):303-7. PubMed PMID: 22131128.
 8. Singh SP, Wahajuddin, Ali MM, Kohli K, Jain GK. Liquid chromatography-mass spectrometry method for the quantification of tamoxifen and its metabolite 4-hydroxytamoxifen in rat plasma: application to interaction study with biochanin A (an isoflavone). *Journal of chromatography B, Analytical technologies in the biomedical and life sciences*. 2011 Oct 1;879(27):2845-51. PubMed PMID: 21890435.
 9. Friedman JA, Taylor SA, McDermott W, Alikhani P. Multifocal and recurrent subarachnoid hemorrhage due to an herbal supplement containing natural coumarins. *Neurocritical care*. 2007;7(1):76-80. PubMed PMID: 17634840.
-

Funding for this project was provided by the Canadian College of Naturopathic Medicine

