TRIFOLIUM PRATENSE PHYTOESTROGENIC EFFECTS ON INDIVIDUALS WITH OR AT RISK FOR ESTROGENIC CANCERS

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Abstract

A search and review of current scientific evidence was performed to determine if the phytoestrogenic effect of *Trifolium pratense* (Red Clover) on individuals who have, had or are at risk for estrogenic cancers, are at further risk.

Databases searched include PubMed, PubMed Central, Natural Standards Database, Google Scholar, Cochran Reviews, following relevant links in resource section of articles, polling herbalists from a variety of online interactive groups and personal associations, and a variety of herbal books.

The trend in the evidence suggests that there is an extremely low risk of harm by the phytoestrogens found in *T. pratense*. Studies show its relative safety, even for those individuals with a history of estrogenic cancers.

Key Words: Red Clover, Trifolium pratense, phytoestrogens, xenoestrogens, isoflavones, isoflavanoids, biochanin A, formononetin, daidzein and genistein, in vivo, human clinical trials, cancer, cancer survivor, breast cancer, uterine cancer, prostate cancer, ovarian cancer, estrogen, estradiol, estrone combined with Boolean search words.

Introduction

Trifolium pratense (Red Clover) is an herb rich in phytoestrogens, containing " plant-based compounds structurally similar to estradiol, capable of binding to estrogen receptors as agonists or antagonists. Red clover was traditionally used to treat asthma, pertussis, cancer, and gout. In modern times, isoflavone extracts of red clover are most often used to treat menopausal symptoms, as an alternative hormone replacement therapy; to treat hyperlipidemia; or to prevent osteoporosis." (Natural Standards Database 2014)

A literature review was conducted on nine different studies to investigate the safety of *T. pratense* for those individuals who have, had or are at risk for estrogenic cancers, including cancers of breast, uterine, ovarian or prostate.

Further research was conducted on the phytoestrogens specific to *T. pratense*, xenoestrogens, and natural estrogens produced in the body. Understanding how each type of estrogen interacts within the body is an important factor when deciding whether or not to supplement with *T. pratense*. Evidence seems to point to its relative safety, despite whether or not the consumer has or had estrogenic-type cancers.

Detailed, long term research studies involving herbal, non-food phytoestrogens, with the exception of soy and flax, are few and far between. Several of the studies on *T. pratense* were found in combination with other phytoestrogenic herbs or foods, mostly soy. There continues to be an uncertainty about the long term effects of phytoestrogenic supplementation surrounding at-risk individuals. Results point to minimal or even no known negative effects on study participants, yet the lengths of the studies did not exceed three years.

Fear and confusion from both cancer survivors and oncologists may lead to avoidance and exclusion of herbs like *T. pratense*, and perhaps unnecessarily so. The intention of this paper is to provide facts so that individuals desiring to use red clover medicinally can make an educated decision while mitigating misinformation or fear.

Means and Methods

Research Thesis

Trifolium pratense phytoestrogenic effects on individuals wit or at risk for estrogenic cancers.

Search and Selection Criteria

Studies were based on the phytoestrogen impact of *T. pratense* in individuals who had a history of or were at risk for estrogenic cancers. The terms used as search criteria on PubMed,

PubMed Central, Natural Standards Database, Google Scholar, Cochran Reviews were Red Clover, *Trifolium pratense*, phytoestrogens, xenoestrogens, isoflavones, isoflavanoids, biochanin A, formononetin, daidzein, genistein, *in vivo*, human clinical trials, cancer, cancer survivor, breast cancer, uterine cancer, prostate cancer, ovarian cancer, estrogen, estradiol and estrone, combined with Boolean search words.

A large number of articles were found using these terms in various combinations. To narrow the field, only reputable databases were used. Studies based on human trials were favored in lieu of those based on test tube or animal research. Literature reviews consisting of one meta-analysis of 10 randomized control studies, one observational study, two case controlled studies, two systemic reviews, four clinical trials, and one case report were chosen.

Relevant links in resource sections of articles were followed for further research, as well as an informal survey of herbalists from online interactive groups and personal associations. A variety of herbal books were referenced, such as *Medical Herbalism* by David Hoffmann and *Herbal Constituents* by Lisa Ganora.

In addition, email correspondence was conducted between the author and Juliette Blankenspoor, who is an author, clinical herbalist and owner of the Chestnut School of Herbal Medicine in Asheville, North Carolina.

Data Analysis

All articles were analyzed to determine if there was consistency in the population, randomization, data collection and outcome measures as well as to determine if they supported the research thesis. Although there was some variation between the studies, a focus on the hormonal effects of the isoflavones in *T. pratense* consistently appeared.

Cases and Controls with Results

In evaluating and exploring available studies on *T. pratense* and the estrogenic effects on human subjects, cross reference strategies were used. Any research based on theory vs. actual human study was noted. Only studies involving humans with some kind of relationship to estrogenic cancers were chosen.

Study One: "A three year, randomized, double-blind, placebo-controlled pilot trial study was conducted with in healthy women aged 35-70 years, with at least one first-degree relative with breast cancer. Subjects taking either red clover isoflavones or a placebo were assessed clinically, blood samples were taken every six months, and a mammography, bone density and transvaginal ultrasound (postmenopausal women only) was conducted once per year.

No significant differences in breast density, endometrial thickness, serum cholesterol, follicle stimulating hormone levels and bone mineral density were detected between those taking red clover isoflavones and placebo.

In postmenopausal women, some significant differences in bone marker levels were seen between active and placebo groups, at six months and at 12 months. The adverse event profile was similar across all red clover isoflavone and placebo groups.

This study concluded that treatment with red clover isoflavones is safe and well-tolerated in healthy women and did not adversely affect breast density, skeletal strength or cardiovascular status. In postmenopausal women, endometrial status was not adversely affected. The adverse event profile was similar between red clover isoflavones, and placebo and endocrine status did not differ" (Powles TJ, et al, 2008).

Study Two: "A meta-analysis of 8 randomized control studies, 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 source. 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" (S Vadeboncoeur of the CAM-Cancer Consortium 2013).

Study Three: A study (Health, Eating, Activity, and Lifestyle aka: "HEAL") was conducted among 767 breast cancer survivors, and found that 38 women in the study who were using red clover supplements were less likely to report night sweats, but there was no effect on hot flushes or quality of life (S Vadeboncoeur of the CAM-Cancer Consortium 2013).

Study Four: 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 placebo. Red clover's protective effects in cancer prevention have not yet been demonstrated in clinical studies (S Vadeboncoeur of the CAM-Cancer Consortium 2013).

Study Five : 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, endometrial thickness, or breakthrough bleeding compared with placebo (S Vadeboncoeur of the CAM-Cancer Consortium 2013).

Study Six: 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 (S Vadeboncoeur of the CAM-Cancer Consortium 2013).

Study Seven: 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 (S Vadeboncoeur of the CAM-Cancer Consortium 2013).

Study Eight: A systematic review was conducted on breast cancer patients or those at risk for breast cancer. Subjects were given red clover isoflavones (and soy). Assessments were made to evaluate 1) any impact of the risk for primary breast cancer or breast cancer recurrence 2) the impact of isoflavones on surrogate endpoints for predicting breast cancer risk, including circulating estradiol and effects on estrogen responsive tissues such as the breast, endometrial, and vaginal tissues, and 3) the efficacy of isoflavones in treating menopausal symptoms in patients who have undergone breast cancer treatment.

Observational studies had to report on risk of primary breast cancer or breast cancer recurrence associated with soy or red clover consumption compared with non-consumption in a prospective or retrospective design. *In vitro* and *in vivo* studies were excluded due to the high risk for confounding and previous work on natural health products (vitamin A) showing a lack of correlation between preclinical and clinical results. Due to the nature of (soy as a commonly consumed food and) red clover as a non-dietary item, there were limited observational studies of red clover consumption expected or identified.

Powles et al investigated the effect of red clover in 401 women with a family history of breast cancer (at least one first degree relative affected), assessing circulating FSH, endometrial thickness, mammographic density, and bone density. Participants were randomized to receive 40mg red clover isoflavones (Promensil®) or placebo for three years.

Neither of the randomized control studies reported on breast cancer incidence rates, however surrogate markers of estrogenic activity were examined. Atkinson reported no significant changes in estradiol, FSH, or LH over the one year period. No significant changes in mammographic density among both pre- and post-menopausal women; no significant changes in endometrial thickness between groups though neither of these markers are considered to be highly specific or sensitive predictors of breast cancer risk.

Atkinson reported a significant interaction between treatment group allocation and the ESR1 polymorphism with respect to effect on mammographic breast density. It is difficult to predict if or how a possible increase in breast density might affect breast cancer risk among TT carriers.

The only adverse effects reported were most commonly included breast abnormality, "skin related symptoms" (not described), and other minor adverse events, however these were equally distributed between red clover and placebo groups (Powles TJ et al 2008).

Study 9: A systemic review was conducted on (soy and) red clover for efficacy in improving menopausal symptoms in women with breast cancer, and for potential impact on risk of breast cancer incidence or recurrence.

"Evidence on red clover is limited; however existing studies suggest that it may not possess breast cancer-promoting effects" (Fritz, et al 2013).

Discussion

T. pratense, belonging to the pea (legume) family, contains plant-based estrogens called phytoestrogens, specifically isoflavones . The four main types found in *T. pratense*, from highest concentrations to lowest, are formononetin, biochanin A, daidzein and genistein. Most research studies seemed to favor either formononetin or biochanin A. These estrogens have very mild effects on the body compared to xenoestrogens and natural estrogens.

Xenoestrogens are human-made chemical estrogens found in plastics, pesticides, pollution, pharmaceutical drugs such as oral contraceptives, and other toxins we are exposed to regularily. They are considered to be estrogen disruptors, which can alter the natural balance of hormones in the body, often leading to estrogenic imbalances and cancers. These types of estrogens are very aggressive.

Women's bodies produce natural estrogens called estradiol and estrone. Estrogen receptors are found inside cells, and only estrogens or closely-related molecules are able to bind. Phytoestrogens exert a weaker estrogenic effect on cells than endogenous estrogens and xenoestrogens. When receptor sites are occupied with the less estrogenic phytoestrogens, fewer sites are available for the more potent endogenous estrogens or xenoestrogens" (Blankenspoor 2014).

Juliette Blankenspoor's analogy helps the reader further understand how estrogens affect the body: " Imagine a lock on a doorknob (estrogen receptor site), now picture a key (phytoestrogen) fitting into the lock and turning the key. Now imagine a second key coming along (endogenous estrogen); it can't fit into the lock because there's already a key there, blocking its way (phytoestrogen). The phytoestrogen key opens the door gently, while the

endogenous estrogen would cause the door to fling open with wild abandon. Why do we want to gently open the door? Because most modern women have estrogen dominance, or a relative imbalance of estrogen to progesterone—turning down the estrogen dial by slowly opening the door is a good thing ” (Blankenspoor 2013).

Conclusions and Recommendations

Although *Trifolium pratense* contains phytoestrogens, they have a much more mild effect than other estrogens to which we are exposed. In fact, having a healthy plant estrogen in a cell receptor may prove protective to the body from more harmful and stronger xenoestrogens, which can mutate cells and lead to cancer.

Recommendations for further research on *Trifolium pratense* in relation the phytoestrogen impact on the body, should be based on human subjects with long term follow up to monitor potential reoccurrence of estrogenic based cancers. Studies on *T. pratense* used in whole plant form, harvested at the same time of year to ensure high concentrations and constancy of isoflavone constituents are favored over research conducted with isolated active constituents in standardized supplements, as used in most present day studies.

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