RED CLOVER

Trifolium pratense L.

Family

Fabaceae.

Parts Used

Flower.

Description

Red clover is a perennial, pasture plant that is found across both Europe, Asia and America. A member of the Leguminosae (Fabaceae) family, this well known plant has long been valued as a fodder plant for grazing animals.

Red clover has the classic three oval shaped leaves (sometimes four) that form on a slightly hairy, upright stem. The smooth green leaves normally have a 'v' shaped pale coloured centre which is absent in White Clover. The flowers are red to pink or purple and form a dense terminal ovoid or globular heads that are fragrant and contain nectar that is attractive to bees. Clover has a deep tap root which draws nourishment and minerals into the leaves above.

Traditional Use

Red clover has traditionally been used mainly as an alterative or blood cleanser. It was used in cases of cancer and congested skin conditions such as boils and acne. Red clover was also known for its antispasmodic actions and teas made from the blossoms were employed in cases of whooping cough and other spasmodic bronchial conditions.

In Western herbal medicine, red clover has become popular as a reproductive balancing herb due to its isoflavone content.

Constituents

Red clover contains phenolic acids (including salicylic acid and coumaric acids), flavonols, a range of isoflavones - including genistein, daidzein, formononetin and biochanin-A. Red clover also contains volatile oils and is a source of many nutrients including calcium, chromium, magnesium, niacin, phosphorus, potassium, thiamine and vitamin C.

Actions

Phytoestrogen, antispasmodic, alterative, hypotensive, anticancer, diuretic, nutritive tonic.

Pharmacological Activity

Hormone Regulating Activities

Menopause

A randomized, double-blind, placebo-controlled trial of menopausal women who were experiencing at least 35 hot flashes per week was undertaken to compare the efficacy and safety of two supplements derived from red clover with placebo. After a 2 week placebo run-in, 252 participants were randomly assigned to either 82mg or 57mg isoflavones/day or placebo for 12 weeks. The reductions in mean daily hot flash count at 12 weeks were similar for the treatment and placebo groups. In comparison with the placebo group, participants in the higher dose group reduced hot flashes more rapidly. Although the study provides some evidence for a biological effect of red clover, neither supplement had a clinically important effect on hot flashes or other symptoms of menopause[1]

A herbal formula (Phyto-Female Complex) containing black cohosh, dong quai, milk thistle, red clover, American ginseng and chastetree berry was evaluated for the relief of menopausal symptoms. This randomized, double-blind, placebo-controlled trial in 50 healthy pre and post-menopausal women was carried out for three months. The women receiving Phyto-Female Complex reported a significant reduction in menopausal symptoms compared with the placebo group. The effect of treatment improvements in menopausal symptoms increased over time; by 3 months there was a 73% decrease in hot flushes and a 69% reduction of night sweats, accompanied by a decrease in their intensity and a significant benefit in terms of sleep quality. Hot flushes ceased completely in 47% of women in the study group compared with only 19% in the placebo group. There were no changes in findings on vaginal ultrasonography or levels of relevant hormones (estradiol, follicle-stimulating hormone), liver enzymes or thyroid-stimulating hormone in either group.[2]

A study examined the effects on the endometrium of menopausal women before and after six months use of total isoflavone. This non-controlled clinical prospective trial was carried out with 32 post-menopause women who received 80mg/day of isoflavones for six months. They were evaluated at the beginning and end of treatment by transvaginal pelvic ecography, hysteroscopy and endometrial biopsy. Among the 32 participant women, six presented vaginal bleeding and three presented endometrial alteration when compared to the initial exams. Two of the women developed endometrial cell proliferation and one of them endometrial hyperplasia. There were no significant alterations in relation to endometrial thickness. The overall results showed that around 10% of the women presented with endometrial activity.[3]

Interestingly, another three month randomised cross over study found no endometrial issues. This study evaluated the effects of a red clover extract on selected sex hormones and endometrium in post-menopausal women. Combined evaluation demonstrated that supplementation with red clover in contrast to placebo, significantly increased plasma testosterone levels and decreased endometrial thickness, while oestradiol levels remained unchanged. The observed reduction of endometrial thickness suggested the safety of isoflavones in terms of endometrial hyperplasia.[4]

A study assessed the effect of isoflavones from Kudzu and red clover, along with other targeted nutrients on menopausal symptoms and markers of breast cancer and CVD risk. Twenty five menopausal women suffering from severe hot flushes and night sweats completed a 12 week intervention using a combination isoflavone nutritional supplement. A 46% decrease in reported hot flushes, from an average of 9.7 to 5.2 per day was found, while two markers of CVD risk, the ratio of total cholesterol to HDL cholesterol and homocysteine, showed modest

improvement. A proposed marker of breast cancer risk, the ratio of 2-hydroxyestrone to 16 alpha-hydroxyestrone, also showed an improvement.[5]

A nutritional intervention study found that supplementation with purified isoflavones resulted in an increase in urinary isoflavonoid excretion. There was a wide variety of difference in excretion amongst participants and this individual variation was associated with an interaction between intakes of protein and dietary fibre.[6]

The effects of isoflavone supplementation from red clover on cognitive function was examined in post-menopausal women. Thirty post-menopausal women aged over 60 years received an isoflavone rich tablet for 6 months in a randomized, controlled clinical trial. Cognitive function tests were performed at baseline and at the end of isoflavone or placebo therapy. The supplement did not appear to have any significant short-term effects on cognitive function in postmenopausal women.[7]

A study was conducted to examine whether isoflavones were oestrogen promoting or suppressive in breast tissue. The effects of taking a red clover derived isoflavone supplement daily for 1 year on mammographic breast density compared with placebo was evaluated in 205 women. Change in mammographic breast density, serum oestradiol, FSH, LH, menopausal symptoms and lymphocyte tyrosine kinase activity from baseline to 12 months were assessed. Mammographic breast density decreased in both groups but the difference between the treatment and placebo was not statistically significant despite there being a significant interaction between the red clover group and oestrogen receptor (ESR1) activity. There were no statistically significant treatment effects on oestradiol, FSH, or LH (assessed only in postmenopausal women), or on lymphocyte tyrosine kinase activity.[8]

The safety and tolerability of a red clover supplement was examined in women with a family history of breast cancer to evaluate the feasibility of using the supplement for prevention of breast cancer in healthy women with at least one first-degree relative with breast cancer. The three year randomized, double-blind, placebo-controlled trial assessed clinically and blood samples taken for biochemical analysis every six months. Participants also underwent mammography, bone density and transvaginal ultrasound (post-menopausal women only) 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 suggesting that red clover isoflavones are safe and well tolerated in healthy women.[9]

The effects of a red clover derived isoflavone extract on the Ki-67 proliferative marker of endometrial biopsies was assessed in 45 to 50 year old perimenopausal women. The small pilot study did not find that red clover isoflavones had any antiproliferative effects on the endometrium.[10]

The effectiveness and safety of a red clover isoflavone supplement versus placebo on the change in hot flush frequency in postmenopausal women was examined. The RCT trial of 30 menopausal women experiencing more than five flushes per day was undertaken over three months. All received single blind placebo tablets for 4 weeks and were subsequently randomized to either placebo or 80mg isoflavones for a further 12 weeks. During the first 4 weeks of placebo the frequency of hot flushes decreased by 16%. During the subsequent double blind phase, a further, statistically significant decrease of 44% was seen in isoflavones group, whereas no further reduction occurred within the placebo group.[11]

Osteoporosis

Loss of lumbar spine bone mineral content and bone mineral density was significantly lower in women taking an isoflavone supplement than in those taking the placebo. There were no significant treatment effects on hip bone mineral content or bone mineral density, markers of bone resorption, or body composition, but bone formation markers were significantly increased in the intervention group compared with placebo in post-menopausal women. The data suggests that, through attenuation of bone loss, isoflavones have a potentially protective effect on the lumbar spine in women.[12]

Prostate

Isoflavones (mostly derived from soy) have been used widely in men with benign prostatic hyperplasia as they exert weak antiandrogenic actions rather than weak oestrogenic actions.

The hypothesis that DHEA metabolism may be increased in the prostate in the presence of proinflammatory cytokines such as transforming growth factor beta1 (TGFbeta1), and further, whether red clover extract can reverse this effect was tested. This model of endocrine-immune-paracrine interactions in the prostate found that TGFbeta1 greatly increased DHEA effects on testosterone production and epithelial cell PSA production, whereas red clover isoflavones reversed these effects.[13]

The effect of red clover on the prostate, liver function, quality of life, and sexual function in men with an initial elevated prostate-specific antigen (PSA) level and negative prostate biopsy findings was examined during a 1 year treatment period. The average PSA level was reduced by 33% and the mean prostate volume had decreased slightly after 12 months of treatment. The sexual hormone levels did not change throughout the study. A significant increase in all three liver transaminases after 3 months was noted,while prostate symptoms were reduced and sexual function was unchanged by the treatment. The isoflavone extract was well tolerated and caused no side effects.[14]

Another study examined the effects on isoflavones on prostate cancer. There were no significant differences between pre and post treatment PSA, Gleason score, serum testosterone, or biochemical factors in the treated patients. Apoptosis in radical prostatectomy specimens from treated patients was significantly higher than in control subjects. No adverse events related to the treatment were reported. The results suggested that dietary isoflavones may halt the progression of prostate cancer by inducing apoptosis in low to moderate-grade tumours.[15]

The antiproliferative effects of biochanin A (from red clover) was examined in prostate tissue. Biochanin A-regulated genes suggest multiple pathways of action, including the inhibition of prostate cancer cell growth through induction of cell cycle arrest and apoptosis.[16]

Cardiovascular Activities

A study assessed the peroxisome proliferator-activated receptor (PPAR) gamma activation by red clover extract. The PPARgamma binding affinities and the transactivation activities of red clover extracts, isoflavones, and their metabolites were analyzed. The red clover extracts and the compounds genistein and biochanin A were found to be potent PPARgamma ligands and activators. The activity of certain isoflavone metabolites exceeded even that of the antidiabetic drug, rosiglitazone, a known PPARgamma agonist. A standard dose of proprietary red clover extracts could provide theoretically 15% to 30% of the equivalent daily recommended dose of rosiglitazone, making red clover a possible agent for ameliorating the metabolic syndrome.[17]

Endothelial expression of leukocyte adhesion molecules plays a critical role in the development of atherosclerosis and in plaque destabilization, and oestrogen reduces the expression of these pro-atherogenic molecules. Researchers studied the expression of intercellular adhesion molecule-1 (ICAM-1) and of vascular cell adhesion molecule-1 (VCAM-1) in cultured endothelial cells by phytoestrogens from red clover. The extracts genistein and daidzein were shown to inhibit the endothelial expression of ICAM-1 and VCAM-1 induced by bacterial lipopolysaccharide. Red clover extracts were concluded to act as anti-inflammatory and antiatherogenic agents on human endothelial cells and may induce beneficial actions on human vessels.[18]

A double blind, placebo-controlled trial of 177 women examined the intake of red clover derived isoflavones on cardiovascular parameters. There were no differences between treatments for changes from baseline to 12 months in total cholesterol, LDL cholesterol, triglycerides, HDL cholesterol, systolic and diastolic blood pressures, fibrinogen, and plasminogen activator inhibitor type 1 (PAI-1). Although there were potentially beneficial changes in triglycerides and PAI-1 among perimenopausal women consuming isoflavones, the study suggests that isoflavones alone are not responsible for the well-documented effects of soy protein on blood lipids.[19]

The effects of two red clover supplements were compared to placebo with respect to lipids and bone turnover markers in symptomatic menopausal

women. The 12 week trial of 252 menopausal women assessed changes in HDL-cholesterol, serum osteocalcin, and urinary N-telopeptide. Secondary outcome measures were mean changes of total cholesterol, LDL-cholesterol, the ratio of HDL- to LDL-cholesterol, and triglycerides. Compared with placebo, both of the supplements containing isoflavones decreased levels of triglycerides in symptomatic menopausal women, however the effect was small in magnitude. No other differences with placebo were noted.[20]

Another study found no significant effects on total cholesterol, LDL and HDL cholesterol, triacylglycerol, lipoprotein(a), glucose or insulin concentrations. The results indicate that purified isoflavones derived from red clover had no effect on cholesterol homeostasis or insulin resistance in premenopausal women.[21]

A small placebo controlled study found that dietary supplementation with isoflavones did not significantly alter total plasma cholesterol, LDL or HDL cholesterol or plasma triglyceride levels. However, inverse correlations were found between certain isoflavone metabolite excretion and plasma triglyceride levels. The overall results suggest that isoflavone phytoestrogens from red clover do not significantly alter plasma lipids in post-menopausal women with moderately elevated plasma cholesterol levels.[22]

A study examined the two major isoflavones (biochanin & formononetin) in red clover to see if they differ in their effect on LDL cholesterol. Plasma lipids were measured twice at the end of each trial period. Baseline LDL concentrations did not differ significantly between men or women (n=34), nor between those randomised to biochanin or formononetin. However, the biochanin lowered LDL in men but not women.[23]

The possibility that the heightened cardiovascular risk associated with the menopause can be reduced by increasing dietary isoflavone intake was tested in 17 women by measuring arterial compliance. An initial 3 to 4 week run-in period and a 5 week placebo period were followed by two 5 week periods of active treatment with 40mg and then 80mg isoflavones derived from red clover. Arterial compliance, measured by ultrasound as a pressure (carotid artery) and volume (outflow into aorta) relationship, was determined after each period and plasma lipids were measured twice during each period. Arterial compliance rose by 23% relative to that during the placebo period with the 80mg isoflavone dose and slightly less with the 40mg dose. Plasma lipids were not significantly affected.[24]

Another study was undertaken to evaluate the effects of varying doses of phytoestrogens on lipid and bone metabolism in post-menopausal women. The results show that the administration of an isoflavone combination from red clover was associated with a significant increase in HDL cholesterol, a significant fall in apolipoprotein B, and a significant increase in the predominantly cortical bone of the proximal radius and ulna after 6 months of treatment. There was no significant increase in endometrial thickness with any of the doses of isoflavone used. However, results must be viewed in the knowledge that a simultaneously studied control group was not used.[25]

A study aimed to evaluate the effect of isoflavones contained in red clover extracts *(Trifolium pratense)* on menopausal symptoms, lipids and vaginal cytology in menopausal women. Compared with placebo, red clover isoflavone supplementation significantly decreased menopausal symptoms and had a positive effect on vaginal cytology and triglyceride levels.[26]

The effect of one month of isoflavone supplementation (86mg/day red clover derived isoflavones) on insulin-like growth factor (IGF) status was evaluated. The results showed that red clover isoflavones had a positive effect on HDL cholesterol, but at most a small effect on IGF status in pre-menopausal and no effect in postmenopausal subjects.[27]

The cardioprotective properties of the red clover isoflavones biochanin and formononetin were assessed in a randomized, double-blind trial of men and women. In normotensive men and postmenopausal women, red clover isoflavones enriched in formononetin reduced arterial stiffness and total vascular resistance but had no effect on blood pressure.[28]

The effect of isoflavones from red clover on blood pressure and vascular endothelial function in post-menopausal type 2 diabetic women was examined in a small randomized double-blind crossover trial.

Results showed that daytime systolic and diastolic blood pressures were lower during isoflavone therapy compared to placebo. The increase in forearm vascular resistance was significantly greater during isoflavone supplementation than placebo, suggesting an improvement in basal endothelial function. Plasma lipoproteins, glycated haemoglobin and forearm vascular responses to acetylcholine and nitroprusside did not differ significantly between isoflavone and placebo therapy.[29]

The oestrogen receptor (ER beta) has been assigned a crucial role in normal vascular wall function and prostacyclin has been ascribed a beneficial effect on vessel wall physiology. A six month trial looked at the possibility that isoflavones (that have an affinity for ER beta), might promote endothelial prostacyclin production. The results found that the prostacyclin production increased with isoflavone treatment compared to baseline, suggesting that this was one factor in the beneficial cardiovascular effects of phytoestrogens.[30]

Increased insulin-like growth factor concentrations are related to increased colorectal cancer risk and isoflavones have been associated with reduced colorectal cancer risk. A randomized, placebo-controlled, double-blinded, crossover trial examined 8 week supplementation with red clover derived isoflavones (84mg/d) on serum IGF-I concentrations. Isoflavone supplementation did not significantly affect serum concentrations of total IGF, suggesting that increased levels of IGF-I, as observed in many soy trials, are likely due to simultaneous protein supplementation rather than isoflavones.[31]

Indications

- Menopausal symptoms, particularly hot flushes
- Metabolic syndrome and atherosclerosis
- Hypertension
- Skin conditions such as eczema, boils, acne
- Prostate cancer
- Bronchitis and whooping cough
- Osteoporosis

Energetics

Cooling, sweet, salty.

Use in Pregnancy

Not generally recommended in pregnancy due to phyto-oestrogen content and lack of safety data.

Contraindications

There are no known contraindications for the flower head extracts. Concentrated isoflavone extracts should only be used by people with oestrogen-sensitive cancers under professional supervision because of the possible proliferative effects. Additionally, people with conditions that may be aggravated by increased oestrogen levels, such as endometriosis or uterine fibroids, should use this herb under professional supervision only. No randomised controlled trials have addressed the long-term safety of phyto-oestrogens in patients after a diagnosis of breast cancer.

Drug Interactions

Caution with hormone replacement therapy, methotrexate (a chemotherapy agent and immune-system suppressant), tamoxifen (hormonal therapy used to treat breast cancer), anticoagulant/antiplatelet (such as warfarin) and contraceptive drugs. May be beneficial with lipid-lowering drugs – monitor.

Administration and Dosage

Liquid Extract:	1:1
Alcohol:	30%
Weekly Dosage:	10 to 60mL

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