Menopause has only recently been widely recognised by the medical profession as a medical condition manifested by a variety of unpleasant symptoms that may also contribute to the development of other chronic conditions [1]. Epidemiological studies suggest that the low incidence of menopausal symptoms and correlated diseases in Asian women is directly correlated with the high content of food rich in isoflavone phytoestrogens in their diet [2].

Isoflavones are dietary phytoestrogens capable of producing estrogenic effects. They are present in extremely variable concentrations in food in a wide number of forms of which Formononetin, Biochanin, Daidzein and Genistein are the most commonly occurring biologically active forms. Isoflavone are present in pulse-based foods but Red clover is considered their preferred source because it is the only plant containing all four major estrogenic compounds at very high levels [3].

Source

Red clover is a member of the family Leguminosae scientifically known as Trifolium pratense. It is one of the world’s oldest agricultural crops traditionally grown in Europe and the Far East, and more recently in America, as a medicinal herb for a variety of purposes and as a human food providing a source of protein.

It is a biennial or short-lived perennial plant that blooms in the summer with multiple, fragrant, red to purple flowers and leaves that consist of three oval-shaped leaflets with a distinctive, whitish, V-shaped marking.

Activity

Phenolic phytoestrogens have a chemical structure similar to that of steroidal estrogens, enabling them to interact directly with the human Estrogen Receptors (ER) present on all human
Clinical Evidence

A large number of studies have been conducted on over 1,000 women by specialists at universities and teaching hospitals under close ethical supervision, in accordance with the Good Clinical Research Practice guidelines.

Treatment of menopausal symptoms
Several trials, conducted for a minimum period of three months, showed a statistically significant reduction in several menopause symptoms assessed using the Kupperman index including hot flushes, night sweats, anxiety and depression [9].

Vasomotor Symptoms (Hot Flushes)
In two recent double blind placebo controlled studies, 80 mg of Linnea Red clover extract was administered for 12 and 16 weeks treatment to postmenopausal women. A statistically significant reduction (of about 45%) in both the frequency and severity of hot flashes was reported between the treated group and the placebo group [9, 10].
Osteoporosis/Bone Health
The bone preserving properties of Red clover have been examined in several randomized, placebo-controlled trials, demonstrating a positive effect of Red clover on bone mineral density as well as an increase in bone formation markers.

Moreover the loss of lumbar spine bone mineral content was significantly lower, suggesting a potentially protective effect [11].

Anxiety -Vaginal Atrophy -Mastalgia
Red clover derived isoflavones were found to be more effective than placebo in reducing depressive and anxiety symptoms among postmenopausal women with a 77% decrease in the total score on the Hospital Anxiety and Depression Scale (HADS) and an 81% decrease in the score on the Zung’s Self Rating Depression Scale (SDS) [12].

The administration of Red clover isoflavones has also been correlated with a significant decrease in mastalgia symptoms [13], endometrial thickness, uterine blood flow and an improvement in the vaginal maturation index [14].

Cardiovascular health
The vascular effects of Red clover as potential contributors to the cardio protective properties were studied in two 12 week, double-blind, randomised trials on postmenopausal women.

In women with borderline hyperlipidaemia, a significant increase in high-density lipoprotein cholesterol and a reduction in apolipoprotein were observed from baseline to 12 weeks [15,16].

A 12 week, double-blind, randomised, dose-escalating study was conducted to investigate the effects of two dose levels of the Red clover formulation (40 mg and 80 mg) versus placebo on arterial compliance. The differences between Red clover and placebo were significant for both treated groups [17].

Prostate health
A study conducted at the Austria Landesklinikum Thermenregion Baden assess the effect of chronic isoflavone in male patients treated for 1 year with a daily intake of 60 mg of Red clover extract.

The most important finding was a significant reduction in the Prostate-Specific Antigen (PSA) levels [18].

Toxicity and Safety
The active ingredients of Red clover extract were tested for mutagenicity using the Ames test and the micronucleus test. No mutagenic changes were observed at any concentration.

In addition, acute oral toxicity tests carried out on rats revealed no clinical abnormalities in any animal throughout the observation period or in any organs during the autopsy.
# Technical Description

<table>
<thead>
<tr>
<th><strong>Name of the plant</strong></th>
<th><em>Red clover, Trifolium pratense</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Part of the plant used</strong></td>
<td>Aerial parts of the plant</td>
</tr>
<tr>
<td><strong>Chemical definition</strong></td>
<td>Mixture of isoflavones: Biochanin A, Formononetin, Daidzein and Genistein</td>
</tr>
<tr>
<td><strong>Synonyms</strong></td>
<td>Pavine clover, Cow grass</td>
</tr>
</tbody>
</table>

## Structural Formula

- **Formononetin**
- **Genistein**
- **Biochanin A**
- **Daidzein**

## Appearance

Dark green amorphous powder

## Solubility

Very slightly soluble in methanol and organic solvents; insoluble in water

## Identity

- HPLC
- TLC

## Loss on drying

NMT 3 %

## Sulphated ash

NMT 4 %

## Assay

NLT 40% total isoflavon-aglycones as: Biochanin A, Formononetin, Daidzein and Genistein (in which Biochanin A and Formononetin predominate)

## Possible carrier

Maltodextrin

## Microbiology

Complies EP

## Storage

Sealed container and protected from light and moisture
Bibliographic References


