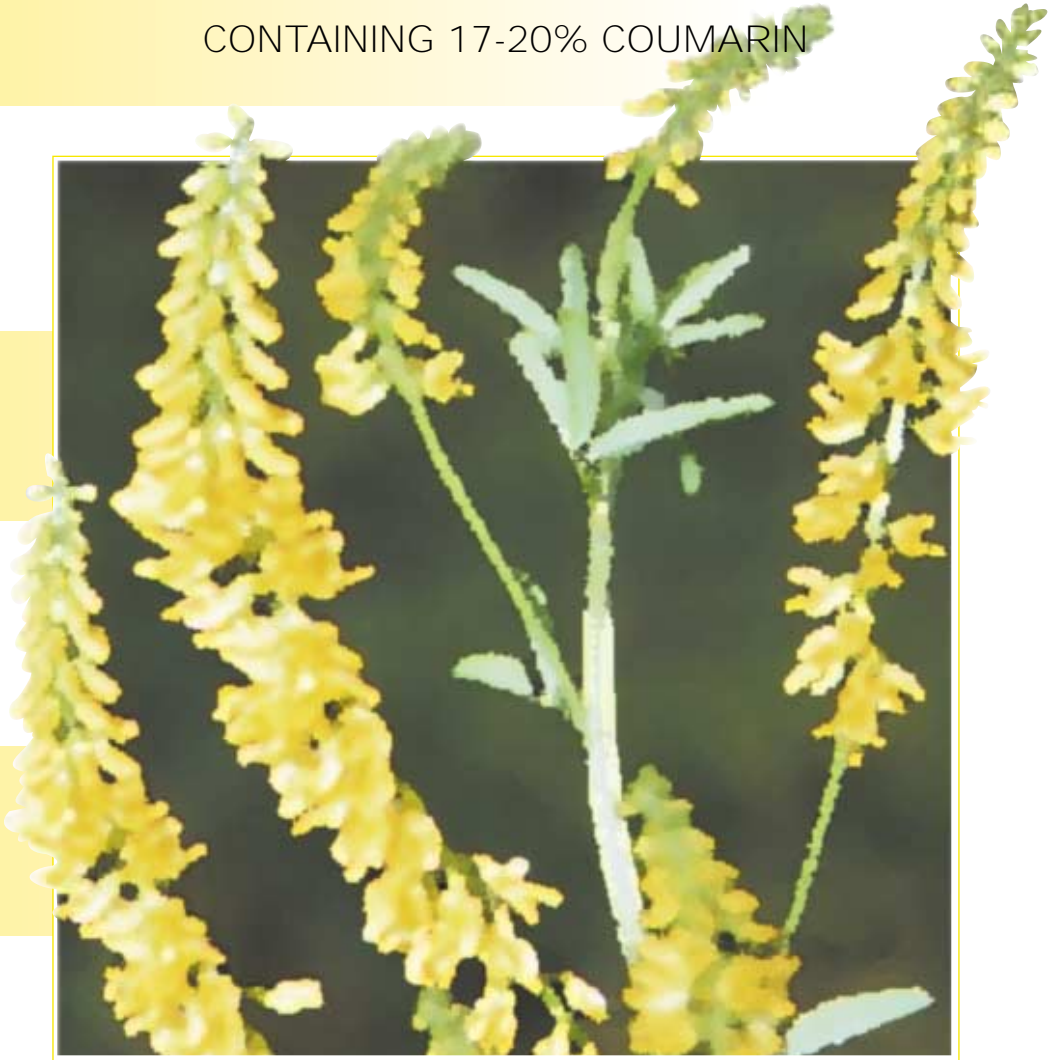


LYMPHASELECT™

MELILOTUS OFFICINALIS STANDARDIZED DRY EXTRACT
CONTAINING 17-20% COUMARIN





BOTANY AND HISTORY

Melilotus officinalis (L.) Pallas (English common names: Yellow Melilot, **Yellow Sweet Clover**) of the Leguminosae family, is a biennial herb with erect stem, 30-250 cm high, commonly occurring along roadsides and in waste areas of Europe and Asia.

It is cultivated for forage, hay, pasture and soil improvement. The leaves are alternate, trifoliate, long-petiolate, and the yellow papilionaceous flowers are arranged in many-blossomed racemes.

The genus name derives from the Latin words mel (honey) and lotus.

This plant, when in flower, has a characteristic sweet fragrance and is a great favorite of bees.⁴⁻⁷

The medicinal properties of *M. officinalis* and other species of Melilotus were known since ancient times. Pliny and Galen (1st and 2nd century A.D.) used to prescribe Melilotus preparations for inflammations, ulcerations and swellings.

Later (15th-19th century) many herbalists and physicians used this plant for similar purposes, and as a digestive, diuretic, expectorant, for eye inflammation, hemorrhoids, phlebitis, varicose veins, ulcers, and for mitigating pain of various origin.^{5,8}

Today an extract of dried flowering tops of *M. officinalis* is the main active component of pharmaceutical preparations for the symptomatic treatment of venous-lymphatic insufficiency.

M. officinalis is mentioned in the French Pharmacopoeia (1989) and in the British Herbal Pharmacopoeia (1996).

Positive monographs on Melilotus preparations have been published by European Scientific Cooperative on Phytotherapy (July 1997) and by the Commission E for Phytotherapeutic Substances of the German Federal Office (March 1986, 1990).

It is known that a high percentage of the population suffers from circulatory disorders both of lymphatic and venous origin.

A deficit of lymphatic function, including drainage and return of interstitial fluid and proteins, is involved in the development of chronic damages associated with lymphedema, a form of high-protein edema.

An increase of capillary filtration and insufficient venous and lymphatic resorption cause edema.

Edema is also one of the most important symptoms associated with chronic venous insufficiency and varicosities in the lower limbs.^{1,2}

In the earliest stages of venous-lymphatic illness topical or systemic pharmacological treatments are used to reduce edema and to alleviate the clinical symptomatology such as pain, heavy legs, itching and cramps.

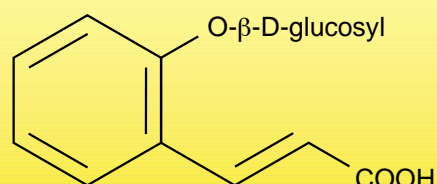
Herbal drug preparations containing coumarins, flavonoids and terpenes are reported to be effective in the symptomatic treatment of venous-lymphatic disorders.^{2,3}

LYMPHASELECT™

MELILOTUS OFFICINALIS STANDARDIZED DRY EXTRACT

M. officinalis contains a series of coumarins (being melilotoside, one of the main components), flavonoids and terpenoids.

M. officinalis dry extract is obtained from the dried flowering tops of this plant and is standardized to 17-20% coumarin.



Melilotoside

BIOLOGICAL ACTIVITIES

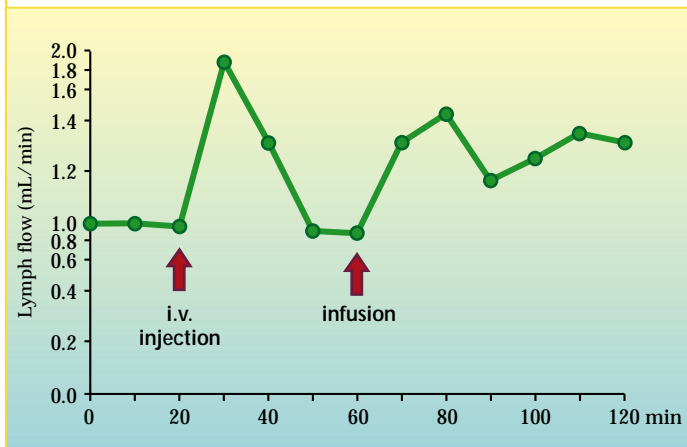
M. officinalis standardized extract and its main active principle coumarin, have been the object of several pharmacological studies which highlighted their interesting pharmacological activities.

Activity on lymph flow

In vitro studies on isolated lymphatic mesentery vessels from guinea pigs, showed that a preparation containing *M. officinalis* extract and rutin (Melilotus-based preparation), as well as pure coumarin had a marked myotropic effect, stimulating the rhythm and tonus of the isolated lymphatic vessels.⁹

In *in vivo* studies the same preparation induced a marked increase in lymph flow in the thoracic duct of narcotized dogs.^{10,11} The effect on acceleration of lymph flow has also been investigated in dog and in man by means of lymphography.¹² Bartoš and Brzek¹³ reported that intravenous administration of Melilotus-based preparation on ten volunteers, increased the lymph flow from the thoracic duct, confirming the lymphokinetic property of this preparation and coumarin. (Fig. 1)

Fig. 1 Mean values of lymph flow in thoracic duct of ten healthy volunteers after the intravenous injection of 6 mg and during the infusion of 15 mg of Melilotus-based preparation, as coumarin.



Anti-inflammatory and anti-edema activities

Shimomura *et al.*¹⁴ reported that an extract of *M. officinalis*, locally applied on the rabbit skin showed protective activity against the increase of capillary permeability induced by formaldehyde and propylene glycol.

Furthermore, the extract and coumarin, subcutaneously injected, reduced the edema caused by formaldehyde in the rat hind paw. The anti-inflammatory and anti-edema properties of coumarin from *M. officinalis* extract (12.5-100 mg/kg, i.p.),

have been confirmed, in several experimental models such as kaolin-induced arthritis, thermal edema, lymphostatic edema and others.¹⁵ Benzopyrones such as coumarin (5,6 benzo- α -pyrone) are well known to be effective against high protein edemas.¹⁶

Recently Borzeix *et al.*¹⁷ reported that Melilotus-based preparation significantly increased venous and lymphatic circulations in rabbits with venous hind leg stasis. (Fig. 2)

Antithrombophlebitic activity

Földi and Zoltán¹⁸ reported that Melilotus-based preparation, tested at intramuscular daily doses of 0.4 mg/kg, as coumarin, mitigated the edematous swelling induced by experimental thrombophlebitis in dogs.

Rutin seemed to potentiate the anti-edema effect of coumarin.¹⁹

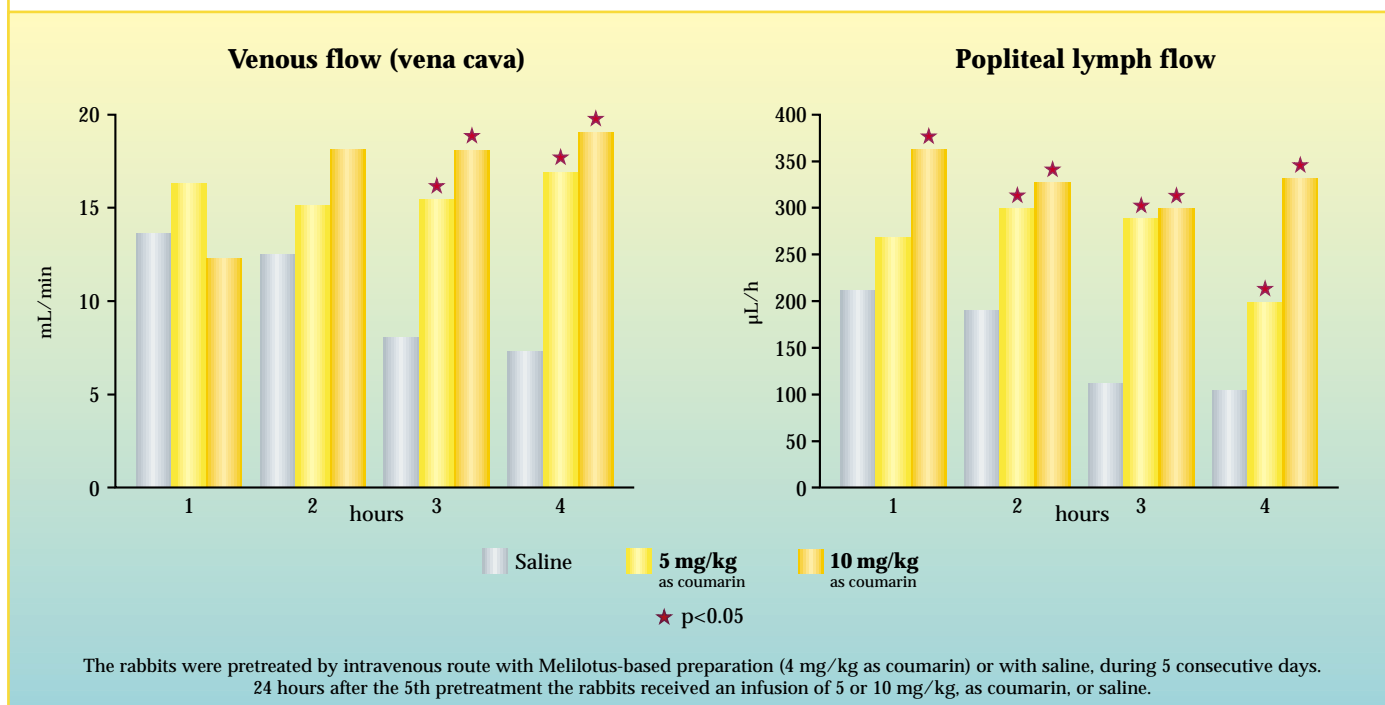


Activity on blood circulation

Coumarin is responsible for the marked increase in blood circulation showed by *M. officinalis* standardized extract.²⁰ It is reported that coumarin from *M. officinalis* extract (5 mg/kg, i.v.) increased capillary blood flow in organs and tissues such as myocardium and striated muscles and had a protective effect against myocardial lesions induced by ischemia in dogs.²¹

Later Sakai *et al.*²² reported that a preparation containing *M. officinalis* standardized extract, rutin and proxiphylline, intravenously injected for 1-4 weeks, in dogs after coronary occlusion, may accelerate the collateral circulation development and reduce the histological damages induced by ischemia in myocardial tissue.

Fig. 2 Effect on venous and lymph flow in rabbits with venous hind leg stasis.



PHARMACOKINETIC AND TOXICOLOGICAL DATA

Pharmacokinetic studies on human healthy volunteers showed that coumarin, administered by oral route, was rapidly absorbed but only approximately 2-6% reached systemic circulation in intact form. This is due to an extensive first pass effect with transformation into 7-hydroxycoumarin and its glucuronide.

The half-life times of coumarin and 7-hydroxycoumarin glucuronide were 1.02 and 1.15 hours respectively. Approximately 90% of the dose was found in the urine as 7-hydroxycoumarin glucuronide.^{23,24} The acute oral LD₅₀ of coumarin in rats has been reported to range from 290 to 680 mg/kg in various rat strains.²⁵

Coumarin has not been reported to be hepatotoxic in baboons or humans.²⁵ Melilotus-based preparation showed to be well tolerated by intraperitoneal route in mice.²⁶ In teratogenicity studies, this preparation as well as coumarin, tested by intravenous route in rabbits at 10 and 100 times the therapeutic dose, did not show any teratogenic effect.²⁷

CLINICAL APPLICATIONS

M. officinalis standardized extract for its activity on blood and lymph flow, found a wide application in the therapeutic treatment of circulatory disorders concerning lymphatic and venous function. Since 1960 clinical studies concerning the therapeutic application of the *M. officinalis* extract²⁸⁻³⁷ were carried out on patients suffering from chronic venous insufficiency, varicosities, thrombophlebitis, hemorrhoids, lymphedema of the lower limbs,

lymphedema associated with mastalgia. The main clinical studies are reported in Table 1.

M. officinalis standardized extract, alone or in association with rutin, was given by oral route at different dosages (as coumarin) ranging from 2 to 60 mg or more, daily.

In the recent literature concerning the management of chronic venous insufficiency, Melilotus-based preparation is recommended for its venotonic and capillary protective activity.^{3,38}

It is also reported to be effective in the treatment of local circulatory troubles associated with fibrocystic mastopathy and with mastalgia.^{39,40}

Borzeix *et al.*¹⁷ reported the results obtained in two unpublished double-blind clinical studies carried out on a total of 414 patients suffering from peripheral venous insufficiency. Oral administration of Melilotus-based preparation improved subjective (heaviness, pain, nocturnal cramps) and objective symptomatology such as edema.

Table 1 *M. officinalis* standardized extract - Main clinical studies.

Number of reference	Number of patients and diagnosis	Period of treatment	Results	Tolerability
29	1158 varicosities 250 thrombophlebitis	30 days	improvement in subjective symptoms ↓ edema, ulcers, pain	
30	25 venous insufficiency (pregnancy)	20 days (minimum)	improvement in subjective symptoms	Very good
31	50 hemorrhoids	10-28 days	↓ anal hemorrhage, edema improvement in subjective symptoms	Very good
32	30 chronic venous insufficiency, varicosities	10-20 days	↓ edema improvement in subjective symptoms	Very good
33	385 chronic venous insufficiency	45 days	↓ edema, ulcers improvement in subjective symptoms	Very good
34	20 mastalgia	10 days/month	↓ breast edema improvement in functional symptoms	Very good
35	55 chronic venous insufficiency	15 days	↓ edema improvement in subjective symptoms	Very good
36	76 lymphedema	6-8 months	↓ edema improvement in subjective symptoms	Very good
37	50 mastalgia	2 months	↓ breast edema improvement in functional symptoms	Good

In all the trials so far cited *M. officinalis* extract showed to be always well tolerated. In a clinical and toxicological study performed on 2173 patients, suffering from chronic infection or cancer,

hepatotoxicity seemed to occur in a very low percentage of patients (0.37%) treated with coumarin. This hepatotoxicity seemed to be idiosyncratic, probably due to a stimulation of the immune system.⁴¹

More recently it has been reported that in several clinical trials in which coumarin (400 mg, daily) was used, a very low incidence of hepatotoxicity was found. Its "possible" plus "probable" rate is about 3 per 1,000.^{42,43}

CONCLUSIVE REMARKS

M. officinalis standardized extract showed to be effective in alleviating the symptomatology associated with lymphedema and with chronic venous insufficiency. In particular its main component coumarin is responsible for anti-edema activity of the extract. Coumarin belongs to the group of benzopyrones which are reported to be effective in reducing high-protein edema.^{2,44} In double-blind, placebo-controlled clinical trials, coumarin showed to be useful in the treatment of postmastectomy lymphedema of the arms and chronic lymphedema of the legs due to various causes.^{45,46} The venotonic and capillary protective activity described for the extract may

in part be ascribed to the flavonoidic component of the extract.

Different mechanisms of action are probably involved in the activity of this extract:

- lymphokinetic activity, demonstrated also in human volunteers on the thoracic channel flow¹³
- increase in lymph fluid drainage due to a direct stimulating effect on the lymphatic vessels⁹
- stimulating effect on macrophages, increasing macrophage phagocytosis and proteolysis⁴⁷
- improvement of venous return quality and speed⁴⁸
- capillary protective activity¹⁴

On the whole the pharmacological and clinical results so far reported indicate that the standardized extract of *M. officinalis*, acting at different levels of the lymphatic and venous systems, may be effective in the symptomatic treatment of chronic venous insufficiency, varicosities, hemorrhoids, thrombophlebitis, post-surgical edema formation, and of severe lymphatic disorders such as lymphedema.

USAGE

The suggested daily dose for chronic use is in the range of 20-50 mg of LYMPHASELECT™

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